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Intramuscular Veriloid (Aqueous Solution) as a Hypotensive Agent. By JOHN H. MOYER, M.D., and IRA JOHNSON, M.D. 477

The Relative Efficacy of Erythromycin (Ilotycin) and of Penicillin in the Treatment of Pneumococcal Lobar Pneumonia. By ROBERT AUSTRIAN, M.D., and ROBERT ROSENBLUM, M.D. 487

Antibiotic Prophylaxis in Chronic Congestive Failure. By LEON V. MCVAY, JR., M.D., DOUGLAS H. SPRUNT, M.D., and THOMAS N. STERN, M.D. 491

A New Approach to Treatment of Brucellosis. By M. RUIZ CASTANEDA, M.D., and C. CARRILLO-CARDENAS, M.D. 504

Selective Pituitary Failure: An Example Characterized by Deficient ACTH and Gonadotrophin Secretion with Intact Thyrotrophin Secretion. By WILLIAM O. MADDOCK, M.D., ROBERT B. LEACH, M.D., SANDER P. KLEIN, M.D., and GORDON B. MYERS, M.D. 509

Liver Biopsy in Rheumatoid Arthritis. By E. R. MOVITT, M.D., and A. E. DAVIS, M.D. 516

Metastatic Carcinoma of the Adrenal. By WELDON K. BULLOCK, M.D., and ALBERT E. HIRST, JR., M.D. 521

Clinical and Laboratory Studies of Infections Due to Pseudomonas Aeruginosa and Pseudomonas Species. By CHESLEY P. ERWIN, M.D., BURTON A. WAISBREN, M.D., and RALPH KRUSE, M.D. 525

Urethral Apoplexy: An Early Symptom of Malignant Hypertension. By SAM C. PASCOE, M.D., and JOHN M. EVANS, M.D. 533

The Action of Hydergine on the Circulation and Metabolism of the Brain in Toxemia of Pregnancy. By MILTON L. MCCALL, M.D., and H. WINFIELD TAYLOR, M.D. 537

Electrocardiographic Pattern Simulating Acute Myocardial Injury. By HAROLD L. OSHER, M.D., and LOUIS WOLFF, M.D. 541

The Effect of Priscoline Upon Normal and Diabetic Glycemia. By MARTIN G. GOLDNER, M.D., and HAROLD ZAROWITZ, M.D. 546

Progress of Medical Science

Therapeutics—Chemotherapy of Tuberculosis. By EDGAR ALSOP RILEY, M.D. 552

Radiology—Protection from Roentgen Rays. By RUSSELL H. MORGAN, M.D. 578

Complete contents on adv. page 10

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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CONTENTS

ORIGINAL ARTICLES

Intramuscular Veriloid (Aqueous Solution) As a Hypotensive Agent 477
By John H. Moyer, M.D., and Ira Johnson, M.D., Houston, Texas.

The Relative Efficacy of Erythromycin (Ilotycin) and of Penicillin in the Treatment of Pneumococcal Lobar Pneumonia 487
By Robert Austrian, M.D., and Robert Rosenblum, M.D., Brooklyn, New York.

Antibiotic Prophylaxis in Chronic Congestive Failure 491
By Leon V. McVay, Jr., M.D., Douglas H. Sprunt, M.D., and Thomas N. Stern, M.D., Memphis, Tennessee.

A New Approach to Treatment of Brucellosis 504
By M. Ruiz Castaneda, M.D., and C. Carrillo-Cardenas, M.D., Mexico, D. F.

Selective Pituitary Failure: An Example Characterized by Deficient ACTH and Gonadotrophin Secretion with Intact Thyrotrophin Secretion 509
By William O. Maddock, M.D., Robert B. Leach, M.D., Sander P. Klein, M.D., and Gordon B. Myers, M.D., Detroit, Michigan.

Liver Biopsy in Rheumatoid Arthritis 516
By E. R. Movitt, M. D., and A. E. Davis, M.D., Oakland, California.

(Contents continued on page 12)

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CONTENTS—(*Continued*)

Metastatic Carcinoma of the Adrenal 521
By Weldon K. Bullock, M.D., and Albert E. Hirst, Jr., M.D., Los Angeles, California.

Clinical and Laboratory Studies of Infections Due to Pseudomonas Aeruginosa and Pseudomonas Species 525
By Chesley P. Erwin, M.D., Burton A. Waisbren, M.D., and Ralph Kruse, M.D., Milwaukee, Wisconsin.

Urethral Apoplexy: An Early Symptom of Malignant Hypertension 533
By Sam C. Pascoe, M.D., and John M. Evans, M.D., Washington, D. C.

The Action of Hydergine on the Circulation and Metabolism of the Brain in Toxemia of Pregnancy 537
By Milton L. McCall, M.D., and H. Winfield Taylor, M.D., Philadelphia, Pennsylvania.

Electrocardiographic Pattern Simulating Acute Myocardial Injury 541
By Harold L. Osher, M.D., Portland, Maine, and Louis Wolff, M.D., Boston, Massachusetts.

The Effect of Priscoline Upon Normal and Diabetic Glycemia 546
By Martin G. Goldner, M.D., and Harold Zarowitz, M.D., Brooklyn, New York.

(Contents continued on page 14)

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A. M. Bongiovanni

Gynecology and Obstetrics
(June and December)
C. Bachman and Franklin L. Payne

THERAPEUTICS

Chemotherapy of Tuberculosis 552
By Edgar Alsop Riley, M.D., New York, New York.

RADIOLOGY

Protection from Roentgen Rays 578
By Russell H. Morgan, M.D., Baltimore, Maryland.

Book Reviews and Notices 587

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NOVEMBER, 1953

ORIGINAL ARTICLES

INTRAMUSCULAR VERILOID (AQUEOUS SOLUTION)* AS A HYPOTENSIVE AGENT

By John H. Moyer, M.D.
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AND

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INSTRUCTOR IN MEDICINE

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A previous report[4] on the treatment of acute hypertensive emergencies dealt with the intravenous use of a biologically standardized and reproducible[3] mixture of ester alkaloids from Veratrum viride, generically designated Alkavervir[6]. Since the hypotensive effect of the veratrum alkaloids is dependent on an action within the cephalic region[7], these agents possess certain advantages over adrenergic and ganglionic blocking agents. They are just as effective in the supine position as in the upright position and postural reflexes are not impaired. Therefore, an extract such as Alkavervir (Veriloid)* is particularly useful for the treatment of hypertensive emergencies in the unconscious or bedfast patient. No serious unfavorable renal, cardiac or cerebral effects have been reported following their use[1,5,8].

There seems to be no question concerning the efficacy of intravenous infusion of Alkavervir (Veriloid) as a method for reducing the blood pressure. It has been used effectively in the treatment of hypertensive crisis and encephalopathy. The administration of Veriloid by continuous infusion is fairly simple if competent and constant nursing supervision is available. It is possible, within 10 to 20 minutes, to reduce a markedly elevated blood pressure to acceptable levels. The patient is then placed on a slow continuous intravenous infusion which must be under constant supervision, with very frequent determinations of the blood pressure, and adjustment of the rate of the infusion. The inconvenience of prolonged therapy of this nature makes an effective intramuscular preparation highly desirable if the blood pressure response is reproducible with a given dose and if this dose can be arrived at by a simple titration procedure; that is, progressively increasing the dose

* Supplied through the courtesy of Riker Laboratories, Inc.

on each injection until the proper one is ascertained. Such a preparation can be given as indicated by the return of blood pressure toward its pre-treatment levels, and requires much less supervision[2] than when the drug is given by continuous intravenous infusion. Since intramuscular Veriloid seemed to have the theoretical advantages mentioned, it seemed important to determine its dosage range and if possible a means of predicting accurately the dose required for any given patient. It was also hoped that the concomitant use of oral and intramuscular Veriloid would result in a lengthening of the interval between intramuscular doses, and thus further simplify the treatment of hypertensive emergencies.

Methods. Solution Intramuscular Veriloid was administered by repeated intramuscular injections to 35 patients with hypertension. The patients were divided into 2 groups. There were 23 patients in Group 1. These patients received only the intramuscular Veriloid. There were 12 patients in Group 2, who received intramuscular Veriloid after they had received the oral form of the drug for several days to 2 weeks. Prior to therapy there was essentially no difference between the 2 groups of patients. Seventeen patients (49%) had malignant hypertension, presenting findings of retinal hemorrhages, and papilledema (Grade 4+ eyegrounds according to the Keith-Wagener classification). Thirteen of the patients (37%) presented evidence of moderate to severe renal damage. This was determined by renal function studies which included phenolsulphonphthalein excretion rate (PSP), blood urea nitrogen, urinalyses, and maximum concentration tests. Five of the patients in Group 1 and 3 in Group 2 presented encephalopathic manifestations.

Initially an attempt was made to determine the intramuscular doses from the amount of drug required to reduce the blood pressure with an intravenous infusion. Subsequent doses were adjusted upward or downward, as indicated, by increments of 0.1 or 0.2 mg. As the study proceeded, it became apparent that it would be equally satisfactory to start with an arbitrary intramuscular dose of 0.6 mg. for the average adult. If necessary, the dose was then increased by 0.2 mg. increments until a definite hypotensive response was obtained. After this hypotensive threshold was reached, further increases of 0.1 mg. were added to each dose until the desired response was obtained. We found that dosages computed on the basis of weight offered little advantage over this arbitrary program. The blood pressure was determined at frequent intervals with a sphygmomanometer and with the patient in the supine position. Atropine and Neo-synephrine were always on hand to combat the possible development of excessive bradycardia (due to vagal stimulation) or extreme hypotensive responses.

The patients in Group 2 were first placed on orally administered Veriloid in doses of 4 mg. given 4 times a day unless nausea and vomiting occurred. When this happened the dose was decreased until the patient did not experience side reactions from the drug. Five patients who experienced nausea and vomiting refused further treatment. After the 12 remaining patients appeared stabilized (after several days to 2 weeks) and repeated blood pressure observations had been recorded, an intravenous infusion of Veriloid was given in order to determine the hypotensive dose by this route when superimposed on previous oral medication. The amount of Veriloid as determined by the intravenous infusion was then used as the initial intramuscular dose which was given the following day, 2 to 3 hours after the oral dose (usually 4 mg.). On subsequent days the intramuscular dose was adjusted upward as in Group 1 until adequate blood pressure reduction was attained.

Results and Discussion. The responses to optimal hypotensive doses of intramuscular Veriloid in the Group 1 patients are recorded in Table 1. A satisfactory reduction in blood pressure was obtained in all patients. An optimal response was considered to be a reduction in blood pressure to approximately 150 systolic and 100 diastolic without producing prohibitive side reactions. There was no evidence of arterial insufficiency (cerebral, coronary) associated with reduction of the blood pressure. We consider this to be significant because of the not infrequent assumption of the compensatory nature of elevated pressures.

It will be noted in Table 1A that when the optimal doses had been ascertained, the duration of the hypotensive response to intramuscular Veriloid

TABLE 1A.—BLOOD PRESSURE AND CLINICAL RESPONSE TO INTRAMUSCULAR VERILOID ALONE

	Control B.P.		*B.P. at Maximum Response**		*Pulse Rate**		*B.P. Reduction*		*Dose*		*Side Effects**	*Diagnosis*	*Fundi ∞*	*PSP*	*Age*	*Symptoms** Improved*
Patient	*S*	*D*	*S*	*D*	*C*	*Dr*	*Onset*	*Duration*	*I.M.*	*I.V. Infusion*						
1	204	140	158	94	84	60	15	360	1.6	0.97	None	HVD	3+	10	42	...
2	266	160	140	90	86	64	10	270	1.7	0.90	Nausea	MHCVD	4+	10	48	yes
3	184	116	154	96	64	50	15	180	1.7	0.90	None	HVD	2+	20	24	yes
4	206	120	146	86	96	88	10	210	1.0	0.60	None	HCVD	3+	10	52	yes
5	224	132	162	92	90	68	15	180	1.7	...	None	HCVD	3+	15	34	...
6	204	140	158	94	84	60	10	?	1.6	...	None	MHCVD	4+	<5	41	...
7	210	120	158	88	68	60	30	360	1.2	...	Nausea	HCVD, HF	1+	10	38	yes
8	218	116	140	54	88	74	10	160	1.0	...	None	HCVD	3+	22	58	...
9	196	116	154	96	70	56	20	210	1.8	...	None	HVD	2+	10	61	...
10	200	150	150	86	100	88	20	210	1.0	...	None	MHCVD	4+	10	31	yes
11	198	128	130	88	80	56	10	240	1.6	...	None	HVD	2+	18	38	...
12	184	124	130	88	76	64	10	240	1.6	1.00	None	MHCVD	4+	20	48	...
13	195	116	155	89	102	88	..	75	1.3	0.84	Hicco-	HVD, HF	1+	20	39	...
14	226	167	161	106	86	70	..	160	2.1	1.21	N & V	MHCVD	4+	5	46	yes
15	206	141	156	96	90	69	..	210	1.5	1.12	None	HVD	2+	10	21	yes
16	215	140	196	86	88	79	..	80	1.4	0.78	Sub. B#	MHCVD,HF	4+	15	38	yes
17	191	125	150	96	82	61	..	210	1.2	0.69	None	HVD, HF	3+	25	46	...
18	225	134	160	100	97	89	..	80	1.8	0.92	Nausea	MHCVD	4+	20	59	...
19	240	140	116	86	82	68	..	150	1.2	0.84	None	HVD	3+	30	42	...
20	260	160	146	96	72	66	..	120	1.8	0.78	None	MHCVD	4+	35	..	yes
21	210	124	98	68	102	88	..	210	1.4	0.54	Dizz.	HVD, SH	2+	22	60	...
22	240	145	156	100	80	60	..	210	0.8	0.54	None	MHCVD	4+	16	72	yes
23	218	148	196	84	88	84	30	180	1.5	....	N & V	MHCVD	4+	5	49	yes
Mean	214	135	151	90	85	70	16	196	1.5	0.84			3+	16	45	

PR —Pulse Rate per minute
S —Systolic
D —Diastolic
BP —Blood Pressure
∞ —Keith–Wagener–Barker Classification
C —Control
Dr —After drug at maximum response
I.M. —Intramuscularly
I.V. —Intravenously
HVD —Hypertensive Vascular Disease

MHCVD—Malignant Hypertensive Cardiovascular Disease
HCVD —Hypertensive Cardiovascular Disease
HF —Heart Failure
PSP —Phenolsulphonphthalein excretion after 20 minutes expressed in per cent of dye injected
SH —Subarachnoid Hemorrhage
Hicco- —Hiccough
* —After Veriloid given intramuscularly
** —Absence of response indicates no improvement or absence of complaints prior to therapy
\# —Sublingual burning

varied from 75 minutes to 360 minutes (6 hours) with an average duration of 3 hours and 16 minutes, and the onset of action occurred within 10 to 30 minutes. This wide range indicates that for therapeutic purposes the intramuscular dosage must be individualized as described above, and the interval between injections must be spaced according to the response of the individual patient. None of the patients obtained an adequate reduction in blood pressure with doses less than 0.8 mg. Therefore, it seems quite satisfactory to give the patient 0.6 mg. initially and to increase the dose in 0.2 mg. increments until the threshold of blood pressure response is reached much like one establishes the dose of insulin in the treatment of diabetes. Subsequent doses can be increased in 0.1 mg. increments until adequate blood pressure reduction is attained. There did not seem to be a consistent relationship between the optimal intramuscular dose and the amount of drug required to reduce the blood pressure to a similar degree by the intravenous infusion. This method for estimating the intramuscular dose should be discarded since it is a cumbersome procedure.

The response to increasing doses of intramuscular Veriloid and the reproducibility of optimal doses on successive days are presented in Table 1B. Reproducibility seemed adequate but it is quite obvious that in the responsive range the dose is quite critical which leaves no room for careless measuring of the amount of drug to be administered since amounts as small as 0.1 to 0.2 mg. made the difference between a good therapeutic result and an excessive blood pressure reduction with prohibitive side reactions. If excessive reduction in blood pressure occurred, the hypotensive response was apt to be markedly prolonged.

Side reactions consisted chiefly of hiccoughs, salivation, nausea and/or vomiting. These were seen in about half of the patients at optimum blood pressure responses, but none were considered to be of serious consequence. Nausea was prominent in 5 patients and severe vomiting was noted in 2 instances. Our results with intramuscular Veriloid are, therefore, quite similar to those obtained with intravenous Veriloid[4]. However, the blood pressure regulation was less consistent, probably a result of the narrow therapeutic index of veratrum and a more variable blood level following the intramuscular route of administration by comparison to the intravenous route. Frequent adjustment of dosage may be necessary to get the best response in any individual patient. Our impression is that once the individual intramuscular dose is established, it is usually not practical to repeat it at less than 4-hour intervals, and in many patients not as often as this. After the optimum dose has been established, subsequent doses of the drug must frequently be reduced as the interval between injections is decreased. After the responsive dose is ascertained, it is frequently easier to maintain the dose constant (optimal) and vary the periods between drug administration (depending on the rapidity with which the blood pressure returns to control levels), so that excessive reduction in blood pressure does not occur because of overlapping blood levels from the previous period of drug administration. If excessive reduction in blood pressure occurs, the optimal dose does not seem to be altered, providing adequate time elapses before the next dose is given. Our experience has demonstrated that the intramuscular administration of Veriloid is a practical therapeutic procedure for hypertensive emergencies and bedfast patients since it reduces the supine blood pressure as well as the erect blood pressure.

The prior oral administration of Veriloid actually shortened the duration (Fig. 1B) of effective blood pressure reduction which was obtainable by an intramuscular injection from an average of over 3 hours to slightly less than 2 hours (Table 1A and 2A). This may be related to the relatively smaller doses of intramuscular solution used in these combined experiments. The somewhat unpredictable rate of absorption of the orally administered Veriloid probably also accounts for this observation. The optimal dose of the intramuscular drug was reduced about 50% by the prior oral administration of Veriloid, but the response was much less reproducible from day to day (Table 2B and Fig. 2).

TABLE 1B.—RESPONSE TO VERILOID ADMINISTRATION INTRAMUSCULARLY—A COMPARISON OF RESPONSIVENESS TO PROGRESSIVELY INCREASING DOSES AND REPEATING THE SAME DOSE ON DIFFERENT DAYS*

	Control B.P.		*B.P. at Maximum Response*		*Pulse Rate*		*B.P. Reduction*		*I.M. Dose (mg.) (Total)*	
Patient	*S*	*D*	*S*	*D*	*C*	*Dr*	*Onset*	*Duration*		*Side Effects*
1#	206	142	170	104	84	68	10	120	1.3	None
	190	128	162	100	84	64	10	130	1.5	Nausea
	204	140	158	94‡	84	60	15	360	1.6‡	None
2#	222	136	220	140	84	84	..	...	1.0	None
	224	134	154	100	80	76	20	240	1.6	None
	224	132	162	92	96	68	30	175	1.6	None
	234	130	188	106	100	72	20	180	1.7	None
	266	160	140	90	86	64	10	270	1.7	Nausea, salivation
	262	154	118	56	88	60	15	360	1.7	Nausea and vomiting
	250	132	208	118	96	92	30	60	1.7	None
	236	136	130	80	84	76	10	300	1.9	Severe vomiting
3#	206	126	180	126	80	76	..	...	1.5	None
	190	116	174	114	76	72	15	30	1.6	None
	188	118	180	112	78	78	..	...	1.7	None
	184	116	154	96	64	50	15	180	1.8	None
	180	110	160	96	72	64	20	115	1.8	None
4#	206	120	146	86‡	96	88	10	210	1.0‡	None
	240	140	116	70	76	56	10	300	1.3	Nausea and vomiting
5#	222	136	218	140	84	88	..	...	1.2	None
	224	134	174	86	80	78	15	205	1.7	None
	224	132	162	92	90	68	15	180	1.7	None
	236	136	206	110	100	72	20	205	1.7	None
6#	206	140	182	108	84	72	30	120	1.2	None
	200	176	176	104	72	64	10	180	1.5	None
	204	140	158	94	84	60	10	?	1.6	None
7#	190	110	186	112	72	64	..	...	1.0	None
	210	120	158	88	68	60	30	360	1.2	Mild nausea
8#	204	126	160	100	96	64	10	180	1.0	None
	218	116	140	54	88	74	10	160	1.0	None
9#	210	126	180	126	80	78	..	...	1.5	
	190	116	178	114	76	68	..	...	1.6	None
	196	116	154	96	70	56	20	210	1.8	None
	190	116	166	100‡	75	64	10	180	1.7‡	None
10#	200	118	150	86‡	100	88	20	210	1.0‡	None
	240	116	116	70	76	60	20	230	1.3	Nausea and vomiting
Mean	214	130	165	99	83	70	16	202	1.5	

Footnotes: ‡ Same dose repeated on 3 separate occasions with similar results
* See Table 1A for key to abbreviation

Here again the determination of the effective hypotensive dose by the intravenous route (when administered while the patient was also taking oral medication) was of little value in de-

TABLE 2A.—BLOOD PRESSURE RESPONSE OF PATIENTS RECEIVING INTRAMUSCULAR VERILOID IN ADDITION TO ORAL VERILOID*

	Control B.P.		*B.P. on Oral Drug*		*B.P. IM + Oral Drug*		*B.P. Reduction*		*Pulse Rate*			*Dose*						
Patient	*S*	*D*	*S*	*D*	*S*	*D*	*Onset*	*Duration*	*C*	*Dr*	*Side Reaction*	*Oral*	*I.V.*	*I.M.*	*Diagnosis**	*Fundi*	*PSP*	*Age*
1–°	212	140	200	128	184	110	20	75	85	70	N & V	12	0.74	1.2	MHCVD	4+	10	36
2–°	212	107	190	100	146	76	10	30	58	48	Sub. B. # Hicco.	14	0.38	0.7	HVD	2+	25	72
3–°	208	134	210	136	184	112	18	75	84	74	None	10	0.46	0.9	MHCVD	4+	15	41
4–°	218	124	200	115	174	105	20	75	98	89	None	8	0.40	0.8	HVD	1+	5	58
5–°	224	138	220	140	168	112	15	45	84	78	Nausea	22	0.76	1.3	MHCVD	4+	12	24
6–°	202	131	180	122	148	70	5	120	92	86	None	14	0.32	0.5	HVD	1+	20	38
7–°	198	130	180	112	164	100	10	75	82	58	None	12	0.38	0.7	HCVD	3+	15	52
8–°	218	142	196	122	112	68	8	90	74	62	N & V	8	0.30	0.7	MHVD	4+	20	41
9–°	226	150	236	140	124	80	12	240	80	62	N + Sal—	16	....	...	MHVD	4+	12	64
10–°	218	112	218	112	148	70	10	180	78	60	Sub. B. #	12	0.60	0.8	HVD	2+	20	39
11–°	226	120	218	120	140	86	15	180	88	80	N & V	16	0.42	1.0	MHCVD	4+	15	56
12–°	230	138	210	132	138	96	30	240	88	68	Nausea	16	0.87	1.0	MHVD	4+	5	42
Mean	216	131	205	123	153	90	14	119	83	70		13	0.51	0.9		3+	15	47

S —Systolic
D —Diastolic
BP—Blood Pressure
C —Control
Dr—Following Drug (Maximum Blood Pressure Response)
* —See Table 1A for key to abbreviations
° —Dose given over 24-hour period

TABLE 2B.—BLOOD PRESSURE RESPONSE TO COMBINED ORAL AND INTRAMUSCULAR VERILOID USING A CONSTANT ORAL DOSE BUT TITRATING THE INTRAMUSCULAR DOSE*

	Control B.P.		*B.P. on Oral Drug*		*B.P. on I.M. + Oral Drug*		*B.P. Reduction*		*PR*			*Dose*		
Patient	*S*	*D*	*S*	*D*	*S*	*D*	*Onset*	*Duration*	*C*	*Dr*	*Side Reactions*	*Oral°*	*I.V.*	*I.M.*
9–°	226	150	206	136	204	128	..	...	84	80	None	16	....	0.6
	...	...	236	140	124	80	12	240	80	62	N & V	16	....	0.8
10–°	218	112	216	96	196	90	..	...	52	52	None	12	0.6	0.5
	...	...	218	114	122	72	10	560	60	48	N & V	12	....	0.7
	...	...	218	112	148	70	10	180	52	44	Sub. B.	12	....	0.8
11–°	226	120	228	136	190	110	20	60	96	88	None	16	0.42	0.7
	...	...	228	118	186	84	10	90	96	84	T in Mo.	16	....	0.9
	...	...	210	120	160	100	10	120	96	88	T. Head.	16	....	1.0
	...	...	218	106	140	54	10	150	88	74	Sub. B.	16	....	1.0
	...	...	218	120	140	86‡‡	15	180	88	80	N & V	16	....	1.0‡‡
12–°	230	138	226	128	200	112	15	60	72	60	None	None	0.87	1.3
	...	...	210	130	158	88	20	360	70	60	None	16	0.32	0.5
	...	...	230	118	190	108	20	90	72	76	None	16	....	0.5
	...	...	214	150	204	130	10	90	72	60	None	16	....	0.6
	...	...	192	116	192	110	..	...	84	76	None	16	....	0.7
	...	...	218	130	198	96	10	60	76	68	None	16	....	0.8
	...	...	210	138	186	110	15	50	80	72	None	16	....	0.9
	...	...	210	132	138	96‡‡	10	240	88	68	Nausea	16	....	1.0‡‡
Mean	225	130	217	124	171	96	13	169	78	69		15	0.55	0.8

* See Table 1A for key to abbreviations
‡‡ Same dose repeated on 3 different days with variable response
° Dose given over 24-hour period

termining the effective dose that should be given initially by the intramuscular route.

A typical study is presented in Figs. 1A and 1B in which the response to Veriloid when administered intravenously is compared with the response following the intramuscular route of administration alone and in combination with orally administered Veriloid.

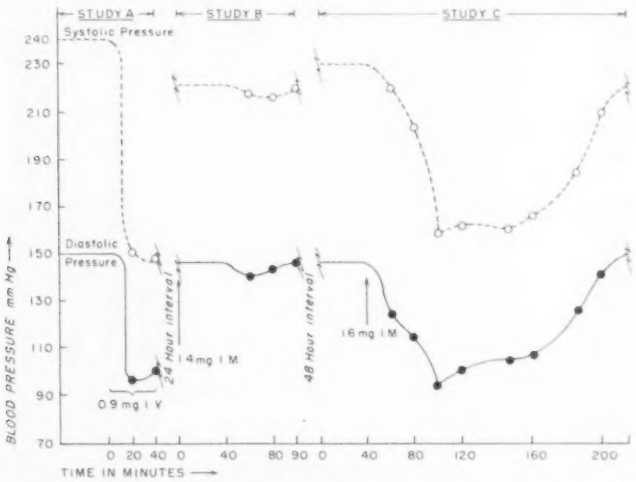

Fig. 1A.—The blood pressure response to an intravenous infusion of Veriloid is presented in Study A. Study B shows a minimal response to 1.4 mg. of Veriloid I.M. When the dose was increased to 1.6 mg., 2 days later the response was quite prominent (Study C).

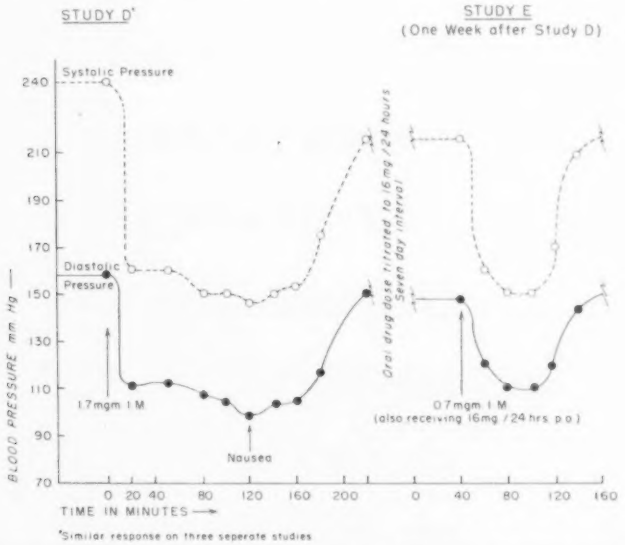

Fig. 1B.—Same patient as in Fig. 1A. There is a marked and sustained reduction in blood pressure for about 4 hours when 1.7 mg. of Veriloid is given I.M. This dose was repeated on 3 separate occasions with similar results. In Study E, intramuscular Veriloid was given in addition to the oral. Although the blood pressure reduction was similar to that in Study D, the response was considerably less sustained.

The maximum response occurs in 10 to 20 minutes after the intravenous infusion; whereas after the intramuscular administration, it occurs in 20 to 90 minutes. In this case example the optimum response after the intramuscular drug occurred on a dose of 1.7 mg. within 20 minutes and the blood pressure remained reduced below the control levels for 4 hours. After maximum blood pressure reduction was obtained, it remained at a rather constant level

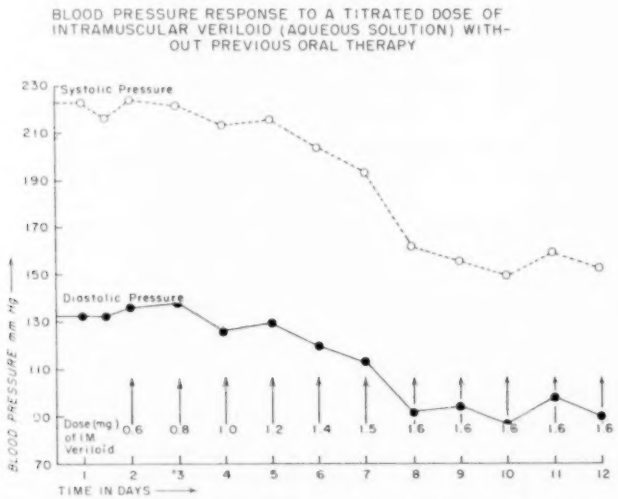
BLOOD PRESSURE RESPONSE TO A TITRATED DOSE OF INTRAMUSCULAR VERILOID (AQUEOUS SOLUTION) WITHOUT PREVIOUS ORAL THERAPY
Systolic Pressure
Diastolic Pressure
BLOOD PRESSURE mm Hg
Dose (mg) of I.M. Veriloid
0.6 0.8 1.0 1.2 1.4 1.5 1.6 1.6 1.6 1.6 1.6
TIME IN DAYS

Fig. 2A.—The maximum blood pressure response following progressively increasing doses of Veriloid given intramuscularly (no concurrent oral medication).

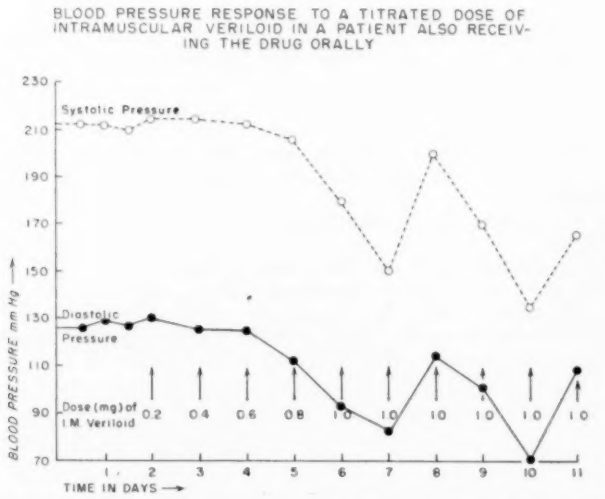
BLOOD PRESSURE RESPONSE TO A TITRATED DOSE OF INTRAMUSCULAR VERILOID IN A PATIENT ALSO RECEIVING THE DRUG ORALLY
Systolic Pressure
Diastolic Pressure
BLOOD PRESSURE mm Hg
Dose (mg) of I.M. Veriloid
0.2 0.4 0.6 0.8 1.0 1.0 1.0 1.0 1.0
TIME IN DAYS

Fig. 2B.—The maximum blood pressure response to a titrated dose of intramuscular Veriloid when given in addition to oral Veriloid. The response is more erratic than with parenteral therapy alone. This is the same patient as presented in Fig. 2A.

for 2½ hours following which it progressively rose to the control levels over the next hour. When the same patient was then placed on 16 mg. of oral Veriloid daily, the pressure was reduced slightly from the control levels. When the intramuscular drug was now given in addition to the oral drug the optimum response occurred on a dose of 0.7 mg. (I.M.) but the blood pressure remained reduced for only 60 minutes following which it rapidly rose to the same level observed prior to the administration of the intramuscular Veriloid.

Summary and Conclusions. Intramuscular Veriloid (aqueous solution) reduces the blood pressure in patients with hypertensive disease. This route of administration simplifies the maintenance of the veratrum-induced hypotension for the treatment of hypertensive emergencies. Combined oral and intramuscular administration did not offer any advantages over intramuscular therapy alone.

It appears that the best approach to establishing the proper dose is to start with a small dose; namely, about 0.6 mg. in the usual case. If this does not produce a satisfactory hypotensive response, succeeding doses should be increased by 0.2 mg. at a time, until a definite response is noted. Further increases of 0.1 mg. may be necessary to achieve the desired degree of hypotensive response. The established intramuscular dose may then be administered at approximately 6-hour intervals (more or less as indicated). In an occasional patient, intervals as long as 12 hours may be necessary between doses. The response of the individual patient must be at all times the guide to the size and the frequency of dosage.

The use of a continuous intravenous infusion to establish the dose of intramuscular drug that would be necessary to adequately reduce the blood pressure was of little value since the relationship was too variable and the necessary dose of the intramuscular drug was too critical (narrow therapeutic index).

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THE RELATIVE EFFICACY OF ERYTHROMYCIN (ILOTYCIN) AND OF PENICILLIN IN THE TREATMENT OF PNEUMOCOCCAL LOBAR PNEUMONIA

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With the advent of erythromycin[7], a bacterial agent[5] with an antibacterial spectrum similar to that of penicillin[3,6] has become available for the treatment of infections in man. The potential role of the newer antibiotic in the therapeutic armamentarium can be assessed in part by comparing its efficacy to that of penicillin in the management of disorders in which the latter drug is of established value. The present report is concerned with the relative merits of erythromycin and of penicillin in the treatment of pneumococcal lobar pneumonia.

Method of Study. All patients with evidence of acute infection of the lower respiratory tract admitted to the medical wards of the University Division, Kings County Hospital, between November 1, 1952, and April 30, 1953, were included initially in the study. On admission, the following laboratory studies were performed: Roentgen-ray of the chest, white blood cell count, blood culture, and a study of the sputum by direct smear, Quellung reaction*, culture and mouse inoculation. The assessment of the severity of illness on admission was based upon the objective historical, physical and laboratory findings listed in Table 1, together with the clinical impression of the hospital physician at the time of his initial examination of the patient.

The patients were divided into 2 comparable groups, one receiving erythromycin** orally, the other penicillin by intermittent intramuscular injection. All patients with history numbers ending in an odd integer received erythromycin while those whose history numbers ended in an even integer were given penicillin.

Patients treated with erythromycin received 400 mg. on admission and 400 mg. every 6 hours thereafter. Treatment was continued until the rectal temperature was below 99.6° F. for 72 hours. Patients receiving penicillin were given 300,000 units of the aqueous sodium salt intramuscularly on admission and every 12 hours thereafter until the rectal temperature was below 99.6° F. for 72 hours.

During the course of illness, the following observations were made: rectal temperature every 4 hours; white blood count at intervals of not longer than 3 days; measurement of hemoglobin once weekly; urinalysis once weekly; Roentgen-ray of the chest before discharge or as otherwise indicated.

All patients admitted with a clinical diagnosis of pneumonia in the period noted above were included initially in this study. Those

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* The capsular typing serum used was made available through the courtesy of Dr. H. D. Piersma, Lederle Laboratories Division, American Cyanamid Company.

** The erythromycin used in this study was supplied by Eli Lilly and Company, through the courtesy of Dr. J. W. Smith.

in whom the diagnosis could not be substantiated by the isolation of a pneumococcus and by roentgenographic demonstration of pulmonary consolidation were excluded subsequently. Excluded also was one patient who should have received penicillin but who was treated with terramycin through error and recovered uneventfully. One patient with a history of sensitivity to penicillin who should have received penicillin according to the protocol was treated with erythromycin and is included with those receiving this drug.

TABLE 1.—CLINICAL AND LABORATORY DATA IN 50 CASES OF PNEUMOCOCCAL LOBAR PNEUMONIA

	Patients given erythromycin		*Patients given penicillin*		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Total Patients:	24	100	26	100	50	100
Male	14	58.3	19	73.1	33	66
Female	10	41.7	7	26.9	17	34
White	12	50.0	14	53.9	26	52
Negro	12	50.0	12	46.1	24	48
Age of Patients:						
Under 40	9	37.5	12	46.1	24	48
40 to 59 years	6	25.0	8	30.8	21	42
Over 60	9	37.5	6	23.1	15	30
Severity of disease:						
Mild	15	62.5	18	69.3	33	66
Moderate	6	25.0	7	26.9	13	26
Severe	1	4.2	0	0	1	2
Critical	2	8.3	1	3.8	3	6
Duration of illness before admission:						
1 to 2 days	6	25.0	9	34.6	15	30
3 to 4 days	8	33.3	7	26.9	15	30
5 to 6 days	5	20.9	8	30.8	13	26
Over 6 days	2	8.3	0	0	2	4
Unknown	3	12.5	2	7.7	5	10
Indications of severity:						
Bacteremia	7	29.2	4	15.4	11	22
Multilobar involvement	1	4.2	1	3.8	2	4
Leukocytes less than 8,000 per c.mm.	3	12.5	2	7.7	5	10
Shock	1	4.2	0	0	1	2
Disorientation	2	8.3	2	7.7	4	8
Alcoholism	3	12.5	3	11.5	6	12
Other*	4	16.7	7	26.9	11	22
Pneumococcal types:						
1 to 8	17	70.8	18	69.3	35	70
Higher types	6	25.0	8	30.8	14	28
Untyped	1	4.2	0	0	1	2
Patients receiving prior treatment:	2	8.3	0	0	2	4
Sensitive to Penicillin:	1	4.2	0	0	1	2

* Cardiac failure, diabetes, narcotic addiction, etc.

Results. Of the 50 patients comprising the study, 24 were treated with erythromycin and 26 with penicillin. Assessed according to the criteria set forth in Table 1, the infections were considered to be of comparable severity in the 2 groups save for the higher incidence of bacteremia among those treated with erythromycin.

The results of therapy are summarized in Table 2. Three deaths occurred in this series of patients. Of the 2 patients treated with erythromycin who succumbed, one was an 82-year-old-

white male admitted on the third day of illness with lobar pneumonia of the left lower lobe and bacteremia due to pneumococcus type 2. His leukocyte count on admission to the hospital was 12,000 per c. mm. and his temperature 102° F. Though somewhat dehydrated, he was not in shock. He died suddenly 4 hours after his initial and only dose of erythromycin. The other patient who received erythromycin and died was a 63-year-old white male diabetic with lobar pneumonia involving the left lower lobe and bacteremia due to pneumococcus type 3. His leukocyte count at the time of hospitalization was 10,200 per c. mm. and his temperature 104.2° F. The patient was treated with erythromycin orally; but, because he was in shock, penicillin, 600,000 units intramuscularly every 6 hours, was administered concomitantly. Despite these and supportive measures, the patient expired 16 hours after entering the hospital. The one patient in the group treated with penicillin who died was a 78-year-old white male hospitalized with uremia, lobar pneumonia of the left lower lobe and bacteremia due to pneumococcus type 3. The leukocyte count was 6,360 per c. mm. and the blood urea nitrogen 144 mg. per 100 cc. Following treatment with penicillin, the patient's temperature fell gradually to normal on the fourth hospital day, but it rose again to 102° F. on the eighth hospital day, and the patient died 24 hours later. Necropsy performed 14 days after death revealed multiple small abscesses in the left lower lobe.

The protocol for treatment with erythromycin was maintained in all patients save one who developed a sterile syn-pneumonic effusion and who received penicillin and streptomycin after the seventh hospital day without evident alteration of her gradual progress to ultimate recovery.

TABLE 2.—RESULTS OF TREATMENT OF 50 PATIENTS WITH PNEUMOCOCCAL LOBAR PNEUMONIA

	Patients given erythromycin		*Patients given penicillin*		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Total Patients:	24	100	26	100	50	100
Duration of fever following start of therapy:						
1 day or less	8	33.3	5	19.6	13	26
2 days	5	20.9	7	26.9	12	24
3 days	3	12.5	1	3.8	4	8
4 days or more	8	33.3	13	50.0	21	42
Duration of WBC greater than 10,000* per c.mm.:						
3 days or less	7	29.2	12	46.1	19	38
4 to 6 days	5	20.9	5	19.6	10	20
7 days or more	4	16.7	6	23.2	10	20
Complications:	4	16.7	4	15.4	8	16
Deaths:	2	8.3	1	3.8	3	6

* Eleven patients did not have a white blood cell count as high as 10,000 per c.mm. during their illness.

Complications occurred with equal frequency in both treatment groups. In each group, 2 patients developed clinical and roentgenographic evidence of pleural effusion which resolved spontaneously. Thoracentesis in one resulted in the recovery of sterile fluid. Resolution of the pneumonic process was delayed longer than 3 weeks in one patient in each treatment group

and multiple abscesses were found at necropsy in the patient dying following treatment with penicillin.

No untoward reactions were noted that could be ascribed with certainty to either chemotherapeutic agent; and, in the dosage employed, erythromycin did not give rise to gastrointestinal symptoms. One possible instance of drug fever following the administration of erythromycin occurred in a 77-year-old white male. After a fall in temperature to normal on the fourth hospital day together with clinically evident improvement, the patient developed remittent fever between 101° F. and 102.6° F. which persisted from the fifth to the seventh hospital day. At this time, it was suspected that he might have drug fever and treatment with erythromycin was discontinued. His temperature fell promptly to normal and he remained afebrile thereafter. Because of the patient's age and general status, it was deemed unwise to readminister erythromycin.

Discussion. The results of this study involving a limited number of patients suggest that erythromycin is a suitable drug for the treatment of pneumococcal lobar pneumonia. The therapeutic responses observed were similar to those noted by Haight and Finland[3] though they are somewhat at variance with those of Bunn[2], who abandoned the use of erythromycin after experiencing 3 unsatisfactory results in a series of 12 patients.

Several properties of erythromcyin merit comment. First, the drug exerts antibacterial activity against a limited number of bacterial species[3,6] and for that reason it should be employed only under conditions where laboratory facilities permit the establishment of an etiologic diagnosis with reasonable certainty. Second, a number of bacterial species, including pneumococcus, may develop *in vitro*, a clinically significant degree of resistance to erythromycin[1,4]. Although clinical failure in the treatment of pneumococcal pneumonia with erythromycin as a result of this phenomenon has not yet been reported, the possibility of such an event makes erythromycin a potentially less satisfactory drug than penicillin. Third, the relative insolubility of erythromycin and the unavailability of a preparation for parenteral administration at the time of this study have made it seem a less suitable medicament for treating critically ill patients who might require the immediate establishment of adequate blood and tissue levels of an antibacterial agent. For these reasons, it is suggested that erythromycin be reserved as an alternative form of therapy for pneumococcal lobar pneumonia, its principal value residing in the fact that it may be administered to patients sensitized previously to penicillin.

Summary. The efficacy of erythromycin has been compared to that of penicillin in the treatment of pneumococcal lobar pneumonia and the results obtained with these antibacterial agents have been similar. The potential value and limitations of erythromycin have been reviewed briefly and in the light thereof, it is suggested that erythromycin be reserved as an alternative form of therapy for pneumococcal lobar pneumonia.

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ANTIBIOTIC PROPHYLAXIS IN CHRONIC CONGESTIVE FAILURE

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Medical, educational and economic advances in the past 10 to 15 years have greatly altered the problems of medicine. Tuberculosis is no longer the leading cause of death[25]; other formerly prevalent infectious diseases such as typhoid fever and malaria have practically disappeared in this country[2,5]. At present, the physician is primarily concerned with the problems of an aging population; that is, with such conditions as cardiovascular disease, malignancy, pulmonary emphysema and diabetes mellitus. Cardiovascular disease is by far the greatest scourge of the current period and is responsible for more deaths than the next 5 most common causes combined[12]. With continued medical progress, the number of persons included in the older age groups should continue to increase; and therefore, diseases of the heart and blood vessels which are especially common in geriatric persons should assume even greater importance.

Infectious diseases, however, have not been eliminated. Indeed, they are tending to re-assume their former position of importance. These conditions are occurring with increasing frequency in the guise of intercurrent complications of chronic degenerative processes. In this new role, bacterial infections (especially those involving the respiratory and renal systems) are directly or indirectly causing the death of countless elderly individuals.

The geriatric cardiac patient possesses a limited cardiovascular reserve. This may have resulted from chronic disease such as rheumatic infection, prolonged hypertension, coronary artery disease, syphilitic involvement or previous bacterial endocarditis. There may have only been the inevitable wear and tear of time. Whatever the mechanism, infections, and particularly those involving the respiratory tract, are prone to precipitate cardiac decompensation in elderly individuals[9,13,14,16,31]. In such instances after the re-establishment of a state of compensation by the use of digitalis, low sodium diet, diuretics and limitation of activity, respiratory infections remain a grave hazard. Although in recent years there has been a remarkable reduction in fatalities resulting from all types of bacterial pneumonia[2], this condition continues to be a serious danger to those past middle life. Despite intensive administration of sulfadiazine, penicillin and streptomycin, 34 cases of acute nontuberculous bacterial pneumonia died in the John Gaston Hospital in 1950. In 8 fatal cases of pneumococcic pneumonia the

average age was 67.4 years with the range being 50 to 82; while in 26 deaths from acute nonpneumococcic pneumonia the average was 66.9 years with the range being 37 to 93. Only 3 patients in the latter group were under 50 years of age. These results emphasize the important prognostic significance of age in pneumonia.

No patients are more susceptible to respiratory infections than those suffering from chronic congestive failure[13]. These individuals frequently have chronic bronchitis and suffer from repeated bouts of nasopharyngitis, acute bronchitis and bronchopneumonia. As a result of chronic pulmonary congestion, drainage is impaired; therefore, secondary bacterial infection is encouraged[33]. Pulmonary infarction is common and together with congestion, stasis, and limited respiratory movement further encourages bacterial infection. In addition, congestive failure causes a reduction in the tone of the gastrointestinal tract with delayed emptying of the stomach; frequently cardiac cirrhosis, hepatic congestion and jaundice are components of the syndrome of chronic failure[9,13,14,16,31]. As a result, the patient suffers from anorexia, nausea, vomiting, flatulence, weight loss, anemia, weakness and reduced resistance. Constipation is usual, diarrhea occasional. Renal complications result in loss of albumin and along with liver involvement and malnutrition tend to produce hypoproteinemia. The summation of these derangements greatly increases susceptibility to infection.

Once pulmonary infection occurs in a patient having chronic congestive failure, a vicious cycle is inaugurated. Bedrest with restriction of activity increases the likelihood of thrombosis and embolism while enhancing pulmonary congestion. Bowel dysfunction (constipation), muscular weakness and anorexia become prominent complaints. Toxemia of infection adds further strain to the failing heart. In addition, renal and hepatic complications are common. The psychic effect of confinement to bed or rigid curtailment of activity in older persons is a well recognized and difficult problem. It is important to recall that next to cardiac failure, the most common cause of death in cor pulmonale is respiratory infection[32]. A recent report emphasized the frequency of pneumonia as a cause of death in rheumatic heart disease.

In the past few years the prophylactic treatment of rheumatic fever has become firmly established[4]. In this instance efforts are primarily directed toward preventing the occurrence of respiratory infections caused by group A beta hemolytic streptococci. Would it be possible, in a similar manner, to reduce the incidence of secondary pulmonic infections in persons having chronic cardiac failure? If this could be accomplished, it would not only extend life but would greatly promote its enjoyment. Economic savings would be considerable. Many of the recently developed antibiotics have a broad spectrum of activity and are effective against numerous Gram-positive and Gram-negative bacteria. Aureomycin is of value in the treatment of acute pneumococcic and nonpneumococcic bacterial pneumonia[24]. Also, *in vitro* methods had established that this antibiotic was active against such common respiratory pathogens as pneumococci, streptococci, staphylococci and even many strains of Friedlander's bacilli *(Klebsiella pneumoniae)*[3,26]. In other studies it was observed that aureomycin was effective in the prophylaxis of rheumatic fever and in the prevention of superimposed respiratory infections in such chronic pulmonary diseases as emphysema and bronchiectasis[19,20]. When large amounts of aureomycin were administered for prolonged periods, very few significant

side effects were noted; no anaphylactoid reactions occurred[17,18,21,22]. With dosage in the range of 0.5 to 1 gm. daily, even annoying gastrointestinal symptoms were minimal[24]. The addition of the methyl and propyl esters of para-hydroxybenzoic acid (Paraben) to this antibiotic was believed to have largely controlled the overgrowth of *C. albicans*[23]. Therefore, it was decided to administser aureomycin for a prolonged period to elderly persons with severe cardiac disease.

The present paper constitutes a report of the long term use of aureomycin as a prophylactic agent in 149 cases of chronic congestive failure. Comprehensive laboratory procedures concerned with the evaluation of alterations in the bacterial flora and with the development of resistant microorganisms are included. In addition, toxicity studies are presented.

Methods. Following a consideration of blood concentrations attained with various amounts of aureomycin, it was decided to employ the following daily regimen: 250 mg. were administered 30 minutes to 1 hour before breakfast and again 2 hours after the evening meal. In 4 hospitalized patients who received this dosage, blood levels ranged from 0.72 to 2.0 mcg. per cc. over a period of 24 hours; in one instance no trace of the antibiotic could be detected. Subsequently 12 ambulatory patients being observed through the Out-Patient-Department were given this medication and disclosed blood levels varying from 0.06 to 4 mcg. per cc. during a period of 16 hours. No evidence of aureomycin could be demonstrated in 2 instances. A review of the literature and of our previous studies, indicated that such blood concentrations should be adequate to forestall the majority of common bacterial infections involving the respiratory tract[3,24, 26]. Previous clinical observations had established that dosage of this magnitude produced very few toxic side effects. Aureomycin containing Paraben (methyl and propyl esters of para-hydroxybenzoic acid) was employed throughout this study.

In an effort to eliminate unintentional bias and so obtain as objective results as possible, placebo capsules* were obtained which were identical in appearance with the aureomycin preparation used in this investigation. Alternate patients received aureomycin and placebo medication.

In this manner neither the patient nor the physician knew which preparation a given individual was receiving. All patients believed that the same medication was administered to every one. By employing this experimental method, a control group was obtained for comparative clinical and laboratory observations.

One hundred and seventy-five patients attending the General Medicine Clinic of the John Gaston Hospital and the University of Tennessee College of Medicine were included in this investigation. These individuals had advanced chronic congestive failure which required the administration of mercurial diuretics 1 to 5 times each week in addition to digitalis, ammonium chloride and a low sodium diet. All patients were from the lowest social and economic strata. Because of failure to return to the clinic, it was necessary to delete 26 cases. Of the remaining 149 persons, 73 were in the aureomycin group and 76 were in the control series. The average age of those in the antibiotic category was 62.3 years as compared with 63.5 years for the controls. Sixty-two of the patients in the aureomycin series were Negroes while 11 were white; 60 of those in the placebo group were Negroes and 16 were white. In the aureomycin category 46 were males and 27 were females as compared with 54 males and 22 females among the controls. The etiology of the cardiac disease in the antibiotic group was as follows: hypertension, 50; coronary artery disease, 14; rheumatic heart disease, 5; syphilis, 3; hypertension and coronary artery disease, 2. A similar review of the control cases revealed: hypertension, 44; coronary artery disease, 21; hypertension and coronary artery disease, 5; rheumatic heart disease, 4; syphilis, 2.

Each patient in this study was examined at monthly intervals in the General Medicine Clinic of the John Gaston Hospital. In addition, every 3 months a comprehensive examination was performed in the Antibiotic Clinic. At that time the following labora-

* The formula for the placebo capsules expressed in mg. per capsule was anhydrous dicalcium phosphate, 689; magnesium stearate, 10; mineral oil, 13; F. D. and C. yellow #5 dye, 1. At a later date this formula was modified to anhydrous dicalcium phosphate, 360; "proflo", 360; magnesium stearate, 10 and mineral oil, 10.

tory procedures were carried out; hematocrit, sedimentation rate; complete blood cell count, urinalysis, nonprotein nitrogen, serum bilirubin, bromsulfalein retention, cephalin-cholesterol flocculation, total and fractional protein, cholesterol and cholesterol esters. An electrocardiogram was obtained every 3 months and roentgenograms were secured as indicated.

Results. The period of observation in this study ranged from 19.5 to 21 months with an average of 20 months. Thirty-four deaths occurred during this investigation; 15 were in the aureomycin group while 19 were in the placebo category. The average age of those who died in the former group was 66 years, in the latter 61 years. Twenty-four deaths (71%) took place in the John Gaston Hospital and were carefully studied; 9 of these were from the aureomycin series and 15 were from the control group. Thirteen fatal cases were examined at necropsy; 5 had received aureomycin while 8 had been controls. Bacteriologic procedures revealed no overgrowth of *Ps. aeruginosa, P. vulgaris,* hemolytic strains of *M. pyogenes* var. *aureus* or of *C. albicans* in any case treated with aureomycin. *Ps. aeruginosa* and *E. coli* were isolated from the blood stream and the lungs in one instance; however, this was a control patient.

A definite reduction in respiratory infections was observed in the antibiotic cases. Bronchopneumonia was the principal cause of the terminal hospitalization in 4 persons from the control group as compared with only one from the aureomycin series. In the antibiotic category, respiratory infections were decreased in frequency by at least 50% in 30 cases, were unchanged in 41 and actually increased in 2 (Table 1). A similar evaluation of the control patients disclosed a reduction of 50% or more in only 4 cases; in 69 there was no change, while a definite increase occurred in 3. Therefore, 7.5 times as many persons sustained a significant reduction in respiratory infections in the antibiotic group as compared with the placebo category. During the course of this study patients receiving aureomycin prophylaxis required 47 hospitalizations because of congestive failure or respiratory infections; this contrasted to 57 in the control group. Hospital days in the antibiotic group were 633; in the placebo category they totaled 701. Bronchopneumonia and acute bronchitis necessitated institutional care in only one case in the aureomycin series but in 4 of the controls.

TABLE 1.—INCIDENCE OF RESPIRATORY INFECTIONS

	No. of Patients	
	Aureomycin Series	*Control Series*
Decreased at least 50%	30	4
No significant change	41	69
Increased	2	3

From April 1, 1953, to May 1, 1953, each patient was asked if he believed that his health had become better, was unchanged or was worse since this study was begun. In the aureomycin group, 36 believed themselves better, 36 regarded themselves as unchanged and 1 considered himself worse (Table 2). Of the controls, 23 thought themselves better, 46 believed themselves unchanged and 7 considered themselves worse. The opinions of patients are notoriously difficult to assess with any degree of accuracy. Nonetheless, in this project all subjects believed themselves to be receiving the same medication; and the physician had no information as to whether a given individual was given aureomycin or the placebo preparation. Furthermore, the duration of this study should have eliminated early psychologic improvement resulting from a new medication. For these reasons, the subjective opinions of the patients in this investiga-

tion would appear to be of definite value.

TABLE 2.—SUBJECTIVE OPINIONS OF PATIENTS FOLLOWING PROPHYLACTIC THERAPY.

	No. of Patients	
	Aureomycin Series	*Control Series*
Better	36	23
No change	36	46
Worse	1	7

During the first 6 months of therapy, increased appetite was noted by 14 persons included in the antibiotic series as contrasted to 3 in the control category. Associated with this decrease in anorexia was improved strength, energy and interest in life. These results were sufficiently striking to stimulate a further investigation along nutritional lines. It was decided to observe the effect of the addition of minerals and multi-vitamins to both categories. Special capsules of a different color (blue) were, therefore, obtained* and substituted for the previous yellow ones. Following the administration of minerals and vitamins, increased appetite was reported by 3 patients in the aureomycin group and by 4 in the control series. Improvement of appetite, therefore, with increase in strength occurred in 17 cases in the antibiotic category as compared with 7 in the control series.

Serial sedimentation rates (Wintrobe, corrected; Rourke-Ernstene technique), were persistently lower in the aureomycin than in the placebo patients (Fig. 1). These findings correlated quite well with the reduced incidence of respiratory infections in those receiving antibiotic medication. Repeated hematocrit determinations disclosed a greater rise in the aureomycin category (Table 3). In this group

TABLE 3.—HEMATOCRIT DETERMINATIONS

	No. of Patients	
	Aureomycin Series	*Control Series*
Increased	46	49
No change	4	4
Decreased	23	23
Average increase	2.7 cc..	1.4 cc.

there was an average increase of 2.7 cc. per 100 cc. during this study as contrasted to only 1.4 cc. per 100 cc. in the controls. These laboratory results corresponded to the improved appetite, strength and energy frequently observed in the antibiotic subjects. A further examination of the hematocrit determinations revealed that prior to the addition of minerals and vitamins (that is, during the first 6 months), there was an average increase in the antibiotic category of 1.3 cc. per 100 cc. as compared with 0.5 cc. per 100 cc. in the placebo patients; during the ensuing 13 months an additional rise of 1.4 cc. per 100 cc. was recorded in the aureomycin series and 0.9 cc. per 100 cc. in the controls. The antibiotic, therefore, appeared to be the most important factor. It is of interest to note that approximately 80% of patients in

*The composition of the vitamin mineral preparation added to both the aureomycin and the placebo compounds was as follows per capsule: Vitamin A (as Acetate), 2500 U.S.P. Units; Vitamin D (Viosterol, 250 U.S.P. Units; Vitamin B_{12}-$_{12}$b, 0.5 microgram as present in concentrated extractives from streptomyces fermentation; Thiamine HCl, 2.5 mg.; Riboflavin, 2.5 mg.; Niacinamide, 7.5 mg.; Folic Acid, 0.5 mg.; Pyridoxine HCl, 0.25 mg.; Ca Pantothenate, 2.5 mg.; Choline Dihydrogen Citrate, 50.0 mg.; Inositol, 25.0 mg.; Ascorbic Acid, 25.0 mg.; Vitamin E (as tocopheryl acetates), 5.0 Units; Rutin, 12.5 mg.; Iron (as $FeSO_4$), 5.0 mg.; Iodine (as KI), 0.25 mg.; Calcium (as $CaHPO_4$), 72.5 mg.; Phosphorus (as $CaHPO_4$), 55.0 mg.; Boron (as $Na_2B_4O_7.10H_2O$), 0.05 mg.; Copper (as CuO), 0.5 mg.; Fluorine (as CaF_2), 0.05 mg.; Manganese (as MnO_2), 0.5 mg.; Magnesium (as MgO), 0.5 mg.; Potassium (as K_2SO_4), 2.5 mg.; Zinc (as ZnO), 0.25 mg.

All medication was obtained through the courtesy of Lederle Laboratories.

both categories preferred the preparations containing vitamins and minerals. The usual explanation given for this was "They just make me feel better than the others." Since the capsules with vitamins were much larger and more difficult to swallow than the previous ones, this preference would appear to be of significance.

The importance of employing a placebo compound became apparent quite early in this study. During the first week 4 patients were referred from the General Medicine Clinic to the Antibiotic Clinic because of nausea and/or vomiting thought to be caused by aureomycin. However, investigation disclosed that 3 of these cases were controls. It was subsequently established that 3 of these individuals had hepatic congestion and gastrointestinal indigestion due to poor compensation, while the fourth was suffering from digitalis intoxication. These results illustrate several problems: (a) the common view that nausea occurring during antibiotic therapy is doubtless caused by that agent, and (b) the difficulty of evaluating gastrointestinal symptoms in chronic congestive failure.

TOXICITY. Using 500 mg. of aureomycin daily, side effects were quite minimal (Table 4). In no instance was it necessary to discontinue medication because of toxicity. Actually nausea and vomiting occurred equally as frequently in the control category as in the antibiotic group. In one instance a patient discontinued medication (aureomycin) because of nausea; however, this symptom did not recur when the preparation containing the antibiotic together with minerals and vitamins was substituted. Of practical in-

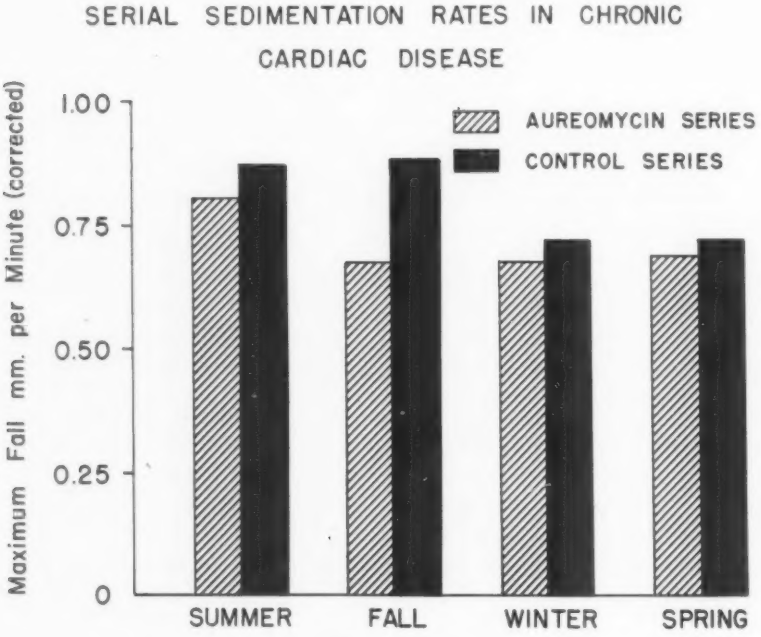

Fig. 1.

TABLE 4.—SIDE EFFECTS TO AUREOMYCIN PROPHYLACTIC THERAPY

	No. of Patients	
	Aureomycin Series	*Control Series*
Nausea	5	5
Vomiting	2*	2
Diarrhea:		
Mild	3	0
Moderate	2	0
Severe	1	0
Pruritus ani	4	0
Pruritus vulvae	0	0
Indigestion	1	1

* One of these patients was relieved by substituting aureomycin - mineral - vitamin mixture for the antibiotic alone.

by the substitution of the combined aureomycin-mineral-vitamin preparation for the antibiotic alone. Pruritus ani was noted by 4 patients receiving aureomycin; it was not reported by any of the controls. Fortunately this complication was mild, transient and required only symptomatic therapy. Novocaine ointment was used for 3 days by one person. All patients were instructed to observe strict hygienic standards, and the importance of preventing anal irritation was stressed.

TABLE 5.—LIVER FUNCTION STUDIES

		Number of Cases			
Determination	*Series*	*Persistently Normal*	*Persistently Abnormal*	*Became Abnormal During Therapy*	*Showed Improvement During Therapy*
BSP retention	Aureomycin	9	16	7	9
	Control	4	18	14	5
Cephalin-cholesterol flocculation	Aureomycin	56	0	0	5
	Control	51	1	7	4
Serum cholesterol	Aureomycin	13	39	10	2
	Control	9	31	16	11
Serum cholesterol esters	Aureomycin	11	23	12	8
	Control	7	26	5	10
Serum bilirubin	Aureomycin	53	5	5	2
	Control	52	5	5	3
Serum albumin	Aureomycin	46	1	16	10
	Control	55	6	6	5
Serum globulin	Aureomycin	43	7	13	11
	Control	39	18	9	8

terest in geriatric patients with chronic illness was the observation that in 6 cases receiving aureomycin, constipation was replaced by normal bowel habits. In another instance aureomycin terminated chronic mild diarrhea and resulted in slight constipation requiring an occasional laxative. All cases of diarrhea reported in this study occurred in the antibiotic group. In one instance, mild diarrhea (2 to 3 stools per day) was relieved

Comprehensive hepatic function tests were carried out initially and thereafter at intervals of 3 months in both groups of cases (Table 5). Laboratory evidence of liver dysfunction was demonstrated in every patient included in the present study. The importance of a battery of determinations in evaluating the various functions of this organ was well illustrated by the results obtained. The serum cholesterol was persistently abnormal in 70 cases

(47%), cholesterol esters in 49 (33%), bromsulphalein retention in 34 (23%), plasma globulin in 25 (17%), serum bilirubin in 10 (6.7%), serum albumin in 7 (4.7%) and cephalin-cholesterol flocculation in 1 (0.7%). Serial determinations of bromsulfalein retention and cephalin-cholesterol flocculation tests indicated improvement in the aureomycin group; this was not apparent in the placebo category. The remaining laboratory procedures disclosed no significant difference between the 2 groups.

Bone marrow preparations were obtained in 22 patients; 11 of these were in the antibiotic group and 11 were controls. No evidence of toxicity due to prolonged antibiotic therapy was observed. These studies were carried out in association with Dr. Alys Lipscomb of the Department of Medical Laboratories and will be reported elsewhere.

BACTERIOLOGIC STUDIES. From February 1, 1953, through May 1, 1953, stool specimens from 43 patients were examined by aerobic culture methods. Blood agar, eosin methylene blue (Difco) and Sabouraud's glucose agar plates were employed. Twenty-four of these cases were from the aureomycin category and 19 were from the controls. The results are represented in Table 6. The 24 specimens from persons receiving prophylactic aureomycin treatment revealed *E. coli* in 21 (88%), *A. aerogenes* in 10 (42%), *Str. faecalis* in 13 (54%), *Str. viridans* in 2 (8%), *M. pyogenes* var. *aureus* in 1 (4%), *Ps. aeruginosa* in 3 (12%), *P. vulgaris* in 16 (67%), nonhemolytic streptococci in 2 (8%) and *C. albicans* in 11 (46%). The 19 stools obtained from control patients yielded *E. coli* in 17 (89%), *A. aerogenes* in 9 (47%), *Str. faecalis* in 14 (74%), *Str. viridans* in 5 (26%), *M. pyogenes* var. *aureus* in 5 (16%), *Ps. aeruginosa* in 1 (5%), *P. vulgaris* in 3 (16%), nonhemolytic streptococci in 5 (26%), and *C. albicans* in 6 (32%). It is apparent, therefore, that the flora in the stools from the 2 groups of patients were quite comparable.

TABLE 6.—FECAL FLORA IN AUREOMYCIN AND CONTROL PATIENTS

	No. of Specimens Revealing Micro-organisms	
Micro-organisms	*Aureomycin Series (24 specimens)*	*Control Series (19 specimens)*
Esch. coli	21	17
A. aerogenes	10	9
P. vulgaris	16	3
Ps. aeruginosa	3	1
Str. faecalis	13	14
Str. viridans	2	5
Nonhemolytic streptococci	2	5
M. pyogenes aureus	1*	3**
M. pyogenes albus	0	2
C. albicans	11	6

* Hemolytic strain
** One hemolytic strain

It should be noted that the single strain of *M. pyogenes* var. *aureus* isolated from the aureomycin patients was hemolytic; of the 2 strains of this organism obtained from the control specimens, one was hemolytic. *P. vulgaris* occurred much more frequently in the antibiotic cases, while *Str. viridans* and nonhemolytic streptococci were isolated more frequently in the controls. Although *C. albicans* was demonstrated more often in those who had received aureomycin, there was no striking difference in incidence; of greater importance was the fact that only one case in both categories revealed significant numbers (3+) of these micro-organisms. These findings confirm the earlier observation that the methyl and propyl esters of parahydroxybenzoic acid (Paraben) prevent the overgrowth of yeast with aureomycin therapy.

BACTERIOLOGIC SENSITIVITY DETERMINATIONS. The possible emergence and subsequent overgrowth of resistant bacteria as a result of antibiotic ther-

apy have been repeatedly emphasized in the current literature[1,6,8,29,30]. While this phenomenon has been reported with all antibiotics, the broad spectrum agents have been regarded as particularly dangerous. For these reasons, *in vitro* sensitivity studies were carried out using organisms isolated from the stools of 15 persons who had received 500 mg. of aureomycin daily for 20 months. These results were compared with those obtained with strains of the same bacteria isolated from 14 control patients. The test tube dilution method was employed to determine the sensitivity of these organisms to aureomycin. Observations were restricted to *A. aerogenes, E. coli, P. vulgaris, Ps. aeruginosa* and *Str. faecalis*. These organisms were selected for investigation because they had been reported as causing serious and even fatal complications to antibiotic therapy[1,6,8,29,30].

The results are recorded in Table 7. Seventy-two strains of bacteria were studied; 41 from antibiotic cases and 31 from the controls. Seven strains of *Str. faecalis* from patients receiving aureomycin were compared with an equal number from placebo cases.

TABLE 7.—IN VITRO SENSITIVITY STUDIES

Concentration Required for Inhibition Mcg. of aureomycin per cc. of medium

Esch. coli	*A. aerogenes*	*P. vulgaris*	*Ps. aeruginosa*	*Str. fæcalis*
		Aureomycin Series		
160.0	40.0	40.0	32.0	40.0
160.0	32.0	40.0	16.0	20.0
160.0	16.0	40.0	8.0	16.0
80.0	16.0	40.0		16.0
64.0	0.3	32.0		4.0
20.0	0.3	32.0		1.3
16.0	0.3	32.0		1.0
8.0		32.0		
4.0		32.0		
4.0		16.0		
1.0				
0.5				
0.5				
0.3				
		Control Series		
32.0	4.0	32.0	16.0	0.3*
16.0	4.0	4.0		0.3*
4.0	2.0	1.0		0.3*
2.0	1.0			0.3*
2.0	1.0			0.3*
2.0	0.5			0.3*
1.0	0.3*			0.3*
1.0				
1.0				
0.5				
0.5				
0.5				
0.3				

* Denotes that organisms were sensitive to less than 0.3 mcg. of aureomycin per cc. of medium.

Definite evidence of the development of resistance following prolonged aureomycin therapy was apparent. Similar, but less striking results were obtained with *E. coli*. However, no significant difference in sensitivity was demonstrated in the remaining bacteria obtained from the 2 categories of subjects.

Discussion. At present more than 7,000,000 persons in this country are

past the age of 65 years; over 1,000,000 have passed the 80 year mark[25]. This represents an increase of 30% in the past 10 years. It is well to recall that the term "geriatric" was introduced less than 40 years ago[25], yet it is now found in every standard textbook of general medicine and in almost every issue of the common medical journals. With the ever expanding number of persons in the older age groups, there has occurred a natural shift in medical interest. The present day physician is becoming increasingly concerned with the diseases of later life: the chronic degenerative conditions. Accompanying the increased longevity of the population as a whole, cardiovascular disease has far outdistanced all other causes of death[12]. Indeed, it is responsible for more deaths than the next 5 leading causes combined. One very crippling form of this disease is chronic congestive failure. The incidence of this disabling process has increased greatly in recent years and should become even more significant in the future. No one who attends the General Medicine or Cardiovascular Clinic of a large hospital can fail to be impressed by this trend.

Patients with chronic congestive failure from any cause are especially susceptible to respiratory infections. Chronic pulmonary congestion combined with impaired drainage, stasis and reduced respiratory motion tends to provide an excellent setting for bacterial invasion. Frequently these elderly individuals are also afflicted with pulmonary disease such as emphysema, bronchiectasis and chronic bronchitis. Aside from congestive failure itself, respiratory infection is the chief cause of death in cor pulmonale. Another important reason for the extreme frequency of respiratory infections in persons with chronic heart failure is the general lack of resistance in such patients. Cardiac cachexia with anorexia, weakness, anemia and malaise is characteristic.

Repeated bouts of acute bronchitis and bacterial pneumonia are especially common in the colder months. These episodes cause further damage to the heart, make compensation even more difficult and by restricting activity introduce the dangerous possibilities of thrombosis and embolism. The obvious economic difficulties do not require discussion.

It was believed that long term antibiotic therapy might reduce the frequency of respiratory infection in chronic cardiacs. This appeared to be a logical extension of prophylaxis as employed in rheumatic fever. Repeated observations had established that prolonged aureomycin treatment using 0.5 to 1 gm. daily was not accompanied by significant side effects and yet was effective in the majority of common pulmonary infections. Therefore, 175 patients having chronic congestive failure were obtained for study. A control series was provided by administering 500 mg. of aureomycin daily to alternate persons while giving the remainder an identical placebo compound. In this way neither the patient nor the physician was aware of which preparation was being received by an individual. The patients believed that every one was given the same medication.

For varied reasons, it was impossible to follow 26 cases. One hundred and forty-nine persons, however, were observed for an average of 20 months. Seventy-three of these were in the aureomycin group and 76 were in the control category. Nineteen deaths occurred in the placebo group as compared with 15 in the antibiotic series. Necropsies were obtained in 13 instances. No evidence of overgrowth by *Ps. aeruginosa*, *P. vulgaris* or hemolytic strains of *M. pyogenes* var. *aureus* was observed. Bronchopneumonia precipi-

tated the final illness in 4 instances in the placebo group but in only one antibiotic case. Likewise, a decrease in respiratory infections of at least 50% was noted in 30 patients in the aureomycin group while a similar effect occurred in only 4 persons in the control series. Thirty-six subjects in the antibiotic category believed themselves better as a result of the present study as compared with only 23 in the placebo category. A single person in the former group regarded himself as worse as contrasted to 7 in the latter category. Repeated sedimentation rates (Wintrobe, corrected; Rourke-Ernstene technique) were consistently lower in those receiving aureomycin prophylaxis. Similarly, a greater rise in hematocrit determinations was noted in the antibiotic subjects than in the controls.

When the present investigation was undertaken, it was believed that 3 major hazards might be encountered. These concerned: 1) the possible occurrence of long term toxicity effects by a broad spectrum antibiotic such as aureomycin, 2) the possible development of resistant strains of bacteria with subsequent proliferation and serious infection and 3) the possible overgrowth of *C. albicans*. Comprehensive clinical and laboratory procedures were carried out in an attempt to evaluate these problems. Toxic side effects to prolonged aureomycin therapy were minimal. In no case was it necessary to discontinue treatment. Nausea and vomiting actually occurred no more frequently among those receiving aureomycin than in the placebo patients. Only diarrhea and pruritus ani were observed much more commonly in the antibiotic group; fortunately, these complications were never serious and required only symptomatic therapy. Similar observations were recorded in other studies[19,20].

Comprehensive hepatic function tests revealed no evidence of toxicity resulting from long term aureomycin therapy. Indeed, serial cephalin-cholesterol flocculation tests and bromsulfalein retention determinations indicated improvement during antibiotic therapy. These findings are of interest in view of divergent reports in the current literature[7,11,15,27,28]. Bone marrow studies were performed in 22 instances: 11 cases in each series; no evidence of a deleterious effect by prolonged aureomycin prophylactic treatment was observed.

Bacteriologic findings in 24 stool specimens from patients who had received 500 mg. of aureomycin for 20 months were compared with those using 19 control specimens. The flora was comparable in both groups though *P. vulgaris* occurred much more frequently in the antibiotic specimens. On the other hand, *Str. viridans* and nonhemolytic streptococci were isolated more commonly from the placebo patients. Overgrowth of *C. albicans* was not demonstrated in the aureomycin specimens. *In vitro* sensitivity studies employing organisms isolated from the stools of 15 persons who had received aureomycin for 20 months were compared with those in which 14 control specimens were used. This phase of the present investigation was restricted to strains of *A. aerogenes, E. coli, P. vulgaris, Ps. aeruginosa* and *Str. faecalis*. *Str. faecalis* and, to a lesser extent, *E. coli* showed the development of significant resistance to aureomycin.

It would appear from these studies that the long term use of aureomycin as a prophylactic agent in chronic congestive failure may be of definite value. It should be emphasized that the goal of this study was prevention, not cure. It was not anticipated that the underlying chronic hypertension, coronary artery disease or valvular destruction would be fundamentally altered. How-

ever, it was believed that any reduction in secondary infection would be of value. A definite decrease in intercurrent infections did occur among those patients receiving aureomycin.

Summary. The increasing number of geriatric patients has emphasized the importance of chronic degenerative processes. A very disabling and common form of cardiovascular disease is long standing congestive failure. Patients afflicted with this condition are very susceptible to disabling and dangerous respiratory infections.

In an attempt to reduce the incidence of intercurrent respiratory infections, 149 cases of chronic congestive failure were observed for an average of 20 months. In many instances the administration of 500 mg. of aureomycin daily significantly diminished the occurrence of infection and caused an increase in appetite, strength and sense of well being.

Evident toxic effects were minimal although these patients were subjected to comprehensive clinical and laboratory examinations. Alterations in the bacterial flora and in the sensitivity of organisms to aureomycin were studied.

While additional observations are necessary, it appears that prolonged antibiotic prophylactic therapy is of value in chronic congestive failure.

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A NEW APPROACH TO TREATMENT OF BRUCELLOSIS

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In spite of recent advances in the treatment of human brucellosis, due to the use of antibiotics, the basis of treatment continues to be as empirical as in the past. A rapid analysis of the achievements in chemotherapy shows interesting facts such as the failure of streptomycin in the human or experimental infections while this drug displays a remarkable antibrucellar activity *in vitro*. This reminds us of similar results with so many substances previously used. On the other hand, aureomycin or terramycin, which appear less effective *in vitro* than does streptomycin, produce rather spectacular suppressive effects not only on the clinical manifestations of the disease but also on the course of the bacteremia. An unexplained synergism, however, was observed when sulfadiazine, of little activity by itself, was used simultaneously with streptomycin. The optimism aroused by early observations in therapy with antibiotics was soon changed into disappointment because of the high rate of recurrences following treatment. Studies on the relationship of *Brucella* to its host have shown that this organism is capable of multiplying within the cytoplasm of certain cells[1,2,8] and it has been our impression that this parasitism is somewhat tolerated. Therefore, it is not likely that certain drugs, introduced as soluble substances, can penetrate the cell, in effective amounts, unless the cell-membrane has been damaged. In this respect the work of Magoffin and Spink[7] has been of interest, showing that even phagocytosis prevents complete inactivation of *Brucella* when exposed *in vitro* to the known antibiotics.

The residual infection resulting from intracellular protection seems to be less persistent after simultaneous treatment with streptomycin or dihydrostreptomycin and aureomycin or terramycin, preferably associated with sulfadiazine. This has been observed in laboratory animals[6,10,11]; and in human brucellosis, according to literature recently reviewed by Shaffer *et al.*[10], combined therapy has produced better results than the treatment with single drugs. However, from the present situation in therapy, one may agree that the only effective way to eradicate *Brucella* would be to introduce the antibacterial agents into the infected cell; a condition which might happen in combined therapy, but which, so far, has not been demonstrated.

Because of the physico-chemical properties of aureomycin and terramycin, we thought of the possibility that a minor fraction of the absorbed or injected drug might precipitate in the plasma due to its low solubility in neutral reaction. If such a thing could happen, the precipitated particles might be phagocytized and eventually reach the lymph-glands, the spleen and other organs: and since it is believed that reticulo-endothelial cells are choice hosts of *Brucella*, there would be a possibility that particles of antibiotic might come in contact with the parasite.

either by direct phagocytosis or phagocytosis of leukocytes carrying these particles.

Working on this assumption, we obtained information part of which has been published[3,9]. There were encouraging results in the treatment of human brucellosis by means of a series of subcutaneous injection of relatively insoluble terramycin in amounts which were exceedingly small in comparison with the massive doses given by oral administration. Our experience has been increased to significant numbers of well controlled cases infected with *Br. melitensis*, the results of which we consider of interest to report in the present note.

Material and methods. The antibiotic used for the present studies was terramycin, which has been recovered from the oral product (marketed in capsules of 250 mg. each) or from alkalinized material destined for intravenous use. When the antibiotic was obtained in capsules, care was taken to purchase at least 100 gm., preferably of the same lot. The powder was treated with distilled water, centrifuged and filtered through a Seitz disc, then the pH adjusted to neutrality by means of sodium hydroxide. The precipitate was separated on sterile filter paper, washed with sterile distilled water and dried at 37° C. Then the powder was ground to particles as fine as 3 to 10 micra and distributed in sterile vials in amounts of 800 mg. each. This material can be kept at ordinary temperature to be used within 3 months. No apparent loss of antibiotic activity has been noticed, but no attempts have been made to use this material after longer periods of time. Similar procedures were followed when alkalinized material was used, except that no filtration was necessary for sterility of the product and that neutralization was made by means of hydrochloric acid.

For use, to a vial containing 800 mg. of precipitated terramycin is added 20 cc. of sterile isotonic sodium chloride solution containing merthiolate (Lilly) in a concentration of 1:10,000. The flask is shaken for uniform dispersion of the powder. Amounts of 2 to 4 cc. are withdrawn in a 5 cc. syringe with an ordinary hypodermic needle 1½ inches in length. The material can be safely injected into the deep subcutaneous tissue of the gluteal region. The injection does not produce immediate pain but on the following days the patients may complain of local irritation. It is customary to massage the site of the injection to favor dispersion of the material. So far, no attempts have been made to administer more than one injection each week and adult patients receive series of 6 to 7 doses corresponding to a total amount of 800 to 1,200 mg. of terramycin. When not in use, the emulsified material must be kept in the refrigerator to prevent resolution of the antibiotic.

SELECTION OF PATIENTS. The majority of the patients submitted to treatment by the present method were adult males and females from the Infectious Ward of the General Hospital and cases observed in an endemic zone 150 miles northwest of Mexico City. There were cases of acute brucellosis as well as protracted forms of undulant fever. Other patients were seen during a recurrence after spontaneous recovery and a minority had had recurrences after treatment with antibiotics. Although, treatment was begun immediately after admission of the patients, regardless of the clinical form or the duration of the disease, only those showing positive blood culture for *Brucella* were selected for the present study.

Since the evolution of the bacteremia seemed to us the best means to judge the effect of the treatment, blood cultures were performed at 15-day intervals. A suitable number of untreated cases were observed for comparison.

The treated and untreated patients were grouped as follows:

Group 1. Forty-four patients of whom 16 had been ill during periods of time ranging from 8 days to 3 months, and the remaining from 4 months to 2 years.

Group 2. Twenty-four cases that had been ill from 15 days to 7 months. These were ambulatory patients.

Group 3. Forty-four patients of whom 31 had been ill from 8 days to 3 months, and the remaining from 4 months to 2 years.

Group 4. Twenty-seven ambulatory cases that had been ill from 15 days to 8 months.

Results. In order to evaluate the present method of treatment with the minimum of misleading information, it was decided that the only reliable factor for comparison between treated and control patients was a series of blood cultures performed by the same method[4] at intervals of 2 weeks. However,

care was taken, in selecting the controls, that these could be comparable not only in the general clinical aspect observed when admitted to the service, but also in the length of time elapsed from the onset of the disease to the time of observation. Ten patients studied recently were allowed to develop the disease without interference. Another group of 34 cases, which added to the former make 44 cases of Group 3, were selected from patients observed in 1947. An additional group of 27 relatively mild cases, also observed in 1947, were considered suitable controls.

TABLE 1.—RESULTS OF SERIAL BLOOD CULTURES PERFORMED IN HUMAN CASES OF BRUCELLOSIS TREATED PARENTERALLY WITH "INSOLUBLE" TERRAMYCIN, AND IN CONTROLS

Serial blood cultures	Group 1 (treated)			Group 3 (control)			Group 2 (treated)			Group 4 (control)		
	Total cases	Cases positive	%	Total cases	Cases positive	%	Total cases	Cases positive	%	Total cases	Cases positive	%
1st culture	44	44	100	44	44	100	24	24	100	27	27	100
2nd 2 weeks	44	8	18	44	41	93	24	4	17	27	26	96
3rd 4 weeks	44	3	7	44	38	86	24	0	0	27	19	70
4th 6 weeks	37*	0	0	44	32	73	—	—	—	—	—	—
5th 8 weeks	31	1	3	44	27	61	—	—	—	—	—	—
6th 10 weeks	28	0	0	38	21	55	—	—	—	—	—	—
From the 4th to 6th month	28	6	21	38	18	47	—	—	—	—	—	—

* Decreasing number of cases resulting from patients that left the Hospital from the 5th week on

Discussion. Our attempts to initiate the present studies with laboratory animals were quite discouraging, particularly because of our lack of a strain of *Br. melitensis* capable of producing detectable infection in mice with the regularity and persistence required for evaluation of a relatively prolonged treatment.

In Table 1 we present the evolution of the blood cultures in the four groups. It may be seen that the incidence of positive cultures in control Group 3 has a rather slow decrease from the first to the third culture to show about 50% positives at the end of the 10th week of observation, not considering what might have occurred with the cases that abandoned the clinic in the 9th week. Control Group 4 shows a course which could be considered parallel to Group 3. On the other hand, the evolution of bacteremia in Groups 1 and 2 shows remarkable differences from the control groups. While the cultures were 100% positive at the beginning of the treatment, the percentages dropped to 18% fifteen days later and still lower by the next blood culture. Practically all the cases remaining in the clinic from the sixth to the twelfth week produced negative blood cultures. In regard to bacteriological recurrences we have found 6 positive cultures out of 27 patients that maintained contact with the clinic from the fourth to the sixth month. With a similar period of observation, 18 out of 38 controls still had bacteremia.

The injection of various doses of precipitated terramycin into the tissues of rats and guinea-pigs gave us an idea of the appropriate amounts which could be safely administered to man. There was observed a certain degree of irritation leading to necrosis when the material was injected under the thin skin of the abdomen. For this reason our patients were injected into the thick subcutaneous layers of the gluteal region. Care has been taken to avoid intramuscular injections. Other

observations of interest made in animals injected with precipitated terramycin were the following: a) Evidence of antibiotic activity was detected after 72 to 96 hours in the serum of rats injected intraperitoneally with 60 mg. of the drug, while particles of antibiotic were still detected in the omentum on the sixth day. b) There was active phagocytosis in the peritoneal cavity, by polymorphonuclear leukocytes and monocytes which showed numerous round vacuoles retaining the shape and size of the injected particles. Often small crystals of antibiotic were found enveloped by the phagocytes. When prints of the cut spleen were made 24 or 48 hours after the injection, it was possible to observe phagocytes with a similar appearance to those found in the peritoneum, and also, monocytes very likely from the spleen, phagocytizing deteriorated polymorphonuclear leukocytes in whose cytoplasm there were forms similar to those found in the peritoneal cavity[3].

These findings indicate that part of the antibiotic deposited in a relatively insoluble form is set in circulation dissolved in the plasma but also that particles of antibiotic may eventually reach the spleen or other organs carried by phagocytes. This is not improbable since known facts show the fate of used phagocytes as well as direct observations concerning the disposition of particles deposited in the peritoneal cavity[5].

Our difficulties in carrying on suitable experimental work in animals have been further handicapped by the very irregular evolution of human brucellosis. The extremes in clinical manifestations are either entire absence of symptoms, in spite of bacteremia, or severely ill patients in whom bacteremia cannot be detected. The observation of 10 cases recently admitted to the Hospital who were given only placebo treatment has been illustrative of the evolution of *melitensis* infection in the average patient. These cases were observed for 3 to 6 months. Hospital care alone was sufficient to bring rapid improvement in the condition of most of the patients, in spite of the fact that in 6 of them the temperature continued above the normal for 3 to 8 weeks. Moreover, in the remaining 4 cases the temperature curve dropped to normal within 15 days just as it was observed in some of the treated cases. In spite of this apparent clinical improvement the blood cultures remained positive in all the cases during a minimum period of 2 months. Because of these observations it was considered that the only dependable criterion by which to judge the effect of the treatment was the evolution of bacteremia. This was particularly important in our cases, since it was not expected to observe dramatic suppressive effects such as are usually seen in cases treated with large doses of antibiotics administered orally.

The effect of the treatment with small doses of antibiotic administered by the subcutaneous route may not be the most adequate to deal with human brucellosis, but, in our opinion, it may be, not only an indication of the possible mechanism of antibrucellar activity of certain drugs, but a rather inexpensive method useful in some countries. It may even be of advantage when oral administration is not desirable. The relatively slow suppression of the clinical manifestations has been modified in our service by an additional treatment for a few days with moderate doses of antibiotics administered by oral route. We are also investigating the possible usefulness of additional series of injections of the same drug as well as combined therapy, hoping to reduce the incidence of recurrences.

Since the present work has been done with patients suffering from *Br.*

melitensis infection, we feel that when evaluating its effect in *abortus* or *suis* infection, it must be kept in mind that *melitensis* infection does not seem to be entirely similar to the other two types of brucellosis.

Summary. The circumstance that *Brucella* has the ability to multiply within certain cells including macrophages, and that soluble antibiotics seem to be incapable of penetrating the cell-membrane, induced us to treat brucellosis by means of relatively insoluble particles of antibrucellar agents which, it was hoped, might come in close contact with the parasite either by concentration of antibiotic, prior to solution, in lymph-glands or the spleen, or perhaps by direct or indirect phagocytosis of the transported particles by reticulo-endothelial cells. Accordingly a number of patients suffering from *Br. melitensis* infection were treated with a series of subcutaneous injections of amphoteric terramycin in amounts not larger than 160 mg. per week. The course of the bacteremia was considered the only reliable criterion for the evaluation of the results. While in control patients the course of bacteremia was uninterrupted for a period of 2 to 3 months, in the treated patients the percentages of positive blood cultures was only 18% fifteen days after the beginning of treatment, to become negative in subsequent cultures. The uniformity of the results leaves no doubt, in our opinion, that this striking difference in the evolution of bacteremia was due to the small doses of the antibiotic administered by the indicated procedure.

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SELECTIVE PITUITARY FAILURE: AN EXAMPLE CHARACTERIZED BY DEFICIENT ACTH AND GONADOTROPHIN SECRETION WITH INTACT THYROTROPHIN SECRETION*

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Hypopituitarism in its classic form is characterized by concomitant failure of gonadal, adrenal cortical and thyroid function. In this complete form it is termed panhypopituitarism. In some cases of panhypopituitarism failure of all three target organs is clinically apparent, whereas in others the signs of failure of one target organ predominates and it is only by means of special procedures that failure of the others is recognized. The syndrome of "pituitary myxedema" described by Means[8] illustrates this situation. In this variant of panhypopituitarism, the features of myxedema predominate, obscuring the underlying panhypopituitarism; and, unless tests of gonadal and adrenal cortical function are carried out, serious therapeutic errors may be committed.

In recent years it has been recognized that in addition to panhypopituitarism, isolated failure of one or more, but not all, anterior pituitary trophic hormones may occur. To this type of dissociated pituitary function the term selective pituitary failure may be applied. The most familiar example of selective dissociation of pituitary secretory activity is the normal prepuberal child, in whom lack of gonadotrophin secretion with adequate output of all other trophic hormones represents the physiologic state. If this type of dissociated pituitary function continues beyond the second decade of life, sexual maturation does not occur and the syndrome of hypogonadotrophic eunuchoidism results. The clinical features and altered physiology of this type of selective pituitary deficiency have been described by Heller and Nelson[3]. Other types of selective pituitary failure were listed by Albright and Elrick[1] in a theoretical discussion in which they classified syndromes that might be expected from isolated alterations in activity of pituitary basophil and acidophil cells. Examples of various combinations of target organ failure were described by Paschkis

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and Cantarow[11] in a report of 17 cases of hypopituitarism, 10 of which were due to pituitary tumor.

It is the purpose of this report to describe a type of selective pituitary failure observed in 4 men in whom failure of gonadotrophin and adrenocorticotrophin secretion was associated with evidence of intact thyrotrophin secretion. The clinical and laboratory features of each case are listed in Table 1. In each patient the clinical manifestations were of long duration (6 to 24 years) and there was no evidence of a local destructive process, such as pituitary tumor, to account for the hypopituitarism. Symptoms appeared following paresis in patient H. D., a long febrile illness in patient K. D., and no known serious illness in patients M. A. and E. H. The evidence for concluding that gonadotrophin and adrenocorticotrophin secretion was deficient and that thyrotrophin secretion was adequate is presented in the following summary of laboratory and clinical features.

Summary of Laboratory and Clinical Features. GENERAL CLINICAL FEATURES. The age of each patient and duration of symptoms are listed in Table 1. All gave similar histories comprising impotence as the initial symptom followed by gradual loss of pubic and axillary hair, progressive weakness, and weight loss of 10 to 20 pounds. Physical examination revealed normal skeletal proportions and absence of cachexia. The patients exhibited the following features in common: abundant, fine, silky scalp hair; intact eyebrows; sparse beard; absent or very scant pubic, axillary and body hair; thin, soft skin; and fine, progeria-like wrinkling of the skin of the face. Sweating was diminished, but present in all. Decrease in pigmentation of the skin and areolae of the nipples was noted in three. In the fourth patient, M. A., there was a questionable history of some diffuse increase in pigmentation at the onset of his illness. Blood pressures were subject to variation, but intermittent hypotension below 90/60 was noted in all patients. The testes were uniformly small and soft, being about half average normal size in each patient.

EVIDENCE OF FAILURE OF GONADOTROPHIN SECRETION. Deficient gonadotrophin secretion was manifested by clinical evidence of marked hypogonadism and laboratory evidence of low urinary gonadotrophin secretion.* In 3 patients the failure of gonadotrophin was considered relatively complete since repeated urinary gonadotrophin assays revealed undetectable levels and each patient had a long history of absolute impotence. Testicular biopsies in these patients revealed completely hyalinized testes; an example is depicted in Fig. 1. Patient K. D. presented findings which were indicative of insufficiency, but not total absence, of gonadotrophin secretion. Repeated urinary assays revealed undetectable to subnormal levels of gonadotrophin. Potency was markedly reduced, but he still had infrequent erections. Testicular biopsy revealed markedly reduced numbers of Leydig cells, reduction in size of seminiferous tubules and arrest of spermatogenesis. Excretion of 17-ketosteroids was reduced, but not to the extent seen in the other patients.

EVIDENCE OF DEFICIENT ACTH SECRETION was indirect, consisting of 1) presence of adrenal cortical insufficiency, and 2) restoration of adrenal cortical function by ACTH therapy.

The clinical features of adrenal cortical insufficiency included marked weakness and intermittent hypotension

*Urinary gonadotrophins were concentrated by ultrafiltration and assayed in immature female rats according to the method of Jungck *et al.*[6], using 3 to 5 rats per assay.

in each patient. Patient M. A. had had repeated Addisonian crises. Patient E. H. had a history of several typical hypoglycemic attacks severe enough to produce unconsciousness. Patient K. D. had experienced similar, but less severe, attacks. The Robinson-Power-Kepler water test was positive in each failure, since hair loss of this degree and 17-ketosteroid excretion this low are not usually seen when adrenal cortical or testicular failure occurs alone.

The response of the adrenal cortex to ACTH therapy conformed to the expected pattern of hypopituitarism in that the response was delayed but

TABLE 1.—SUMMARY OF CLINICAL AND LABORATORY FEATURES IN 4 CASES OF SELECTIVE PITUITARY FAILURE

	H. D.	*M. A.*	*E. H.*	*K. D.*
Age—years	58	54	52	38
Duration of symptoms—years	24	10	6	9
Features attributable to deficient gonadotrophin secretion				
Urinary gonadotrophins	Absent	Absent	Absent	Low to absent
Testicular biopsy: Leydig cells	Absent	Absent	Absent	Markedly decreased
Testicular biopsy: Seminiferous tubules	Completely hyalinized	Completely hyalinized	Completely hyalinized	Spermatogenic arrest
Impotence	Complete	Complete	Complete	Partial
Features attributable to combined gonadotrophin and ACTH deficiency				
Pubic and axillary hair	Absent	Absent	Very sparse	Very sparse
17-ketosteroids—mg. per 24 hours	1.0	0.9	2.1	4.5
Features attributable to deficient ACTH secretion				
Weakness	Marked	Marked	Marked	Marked
Intermittent hypotension	Present	Present with frank crisis	Present	Present
Low fasting blood sugar (below 60 mg. per 100 cc.)	Present	Present	Present	Present
Robinson-Power-Kepler water test	Positive	Positive	Not done	Positive
4-hour ACTH-eosinophil test	222→183	311→250	421→311	152→211
Response to 4 to 5 days ACTH Rᵩ: Eosinophils	350→0	311→11	421→44	152→108→5*
Response to 4 to 5 days ACTH Rᵩ: 17-K. S.	1.0→10.1	0.9→5.0	2.1→7.2**	4.5→10.9
Features indicative of adequate thyrotrophin secretion				
Clinical features of hypothyroidism	Absent	Absent	Absent	Absent
B.M.R. (ave. of 2 or more determinations)	−15%	−11%	−10%	−9%
P.B.I. (micrograms per 100 cc.)	5	6	6***	10.5
24 hr. I^{131} uptake	15%	6%***	12%***	29%

* After 48 hours of a highly purified ACTH preparation, 10 units twice daily.

** This figure was obtained after 12 days of ACTH therapy, a total daily dose of 100 mg. for 8 days and then 25 mg. daily for 4 days.

*** These values were obtained during prolonged ACTH therapy. All other data in this table were obtained before treatment unless specifically noted.

of the 3 patients in whom it was performed, the "A" values ranging from 2.3 to 11.7. Oral glucose tolerance tests revealed hypoglycemia both fasting and three or more hours following ingestion of glucose. The absent or very sparse pubic, axillary and body hair and the very low 17-ketosteroid excretion were attributed to the combination of testicular and adrenal cortical ultimately good. Each of the patients received a test dose of 25 units aqueous ACTH intramuscularly and in none was a significant decrease in numbers of eosinophils observed 4 hours after injection. Continuation of ACTH therapy in doses of 10 to 20 units every 6 hours led to a fall in numbers of eosinophils to almost zero in 3 patients by the fourth or fifth day of therapy. In

the fourth patient, K. D., the number of eosinophils did not decrease with 10 units of a standard ACTH preparation every 6 hours for 4 days, but after 2 days of administration of a highly purified ACTH preparation, 10 units every 12 hours, the number of eosinophils fell to almost zero. A definite increase in 17-ketosteroid excretion occurred in each patient. Only a single determination is listed in the Table; however, serial determinations in patients M. A., H. D., and K. D. revealed a significant increase by the third day, reaching a plateau by the fourth or fifth day of treatment. Subjective improvement was noted in each patient. Twenty units of ACTH every 6 hours proved an excessive dose in 2 patients, leading to an acute psychosis in patient H. D. and clinically evident water retention in patient M. A. These untoward reactions promptly disappeared with reduction in dosage.

EVIDENCE FOR ADEQUATE THYROTROPHIN SECRETION was indirect, consisting of features indicative of normal thyroid function: none of the patients exhibited the symptoms and signs of hypothyroidism; the basal metabolic rate and the protein-bound-iodine levels[15] were within the range of normal in each patient. Radio-iodine uptake was determined* before ACTH therapy in patients H. D. and K. D. and was found to be borderline and normal, respectively. In patients M. A. and E. H., radio-iodine studies, performed after prolonged therapy with ACTH and while the patients were still

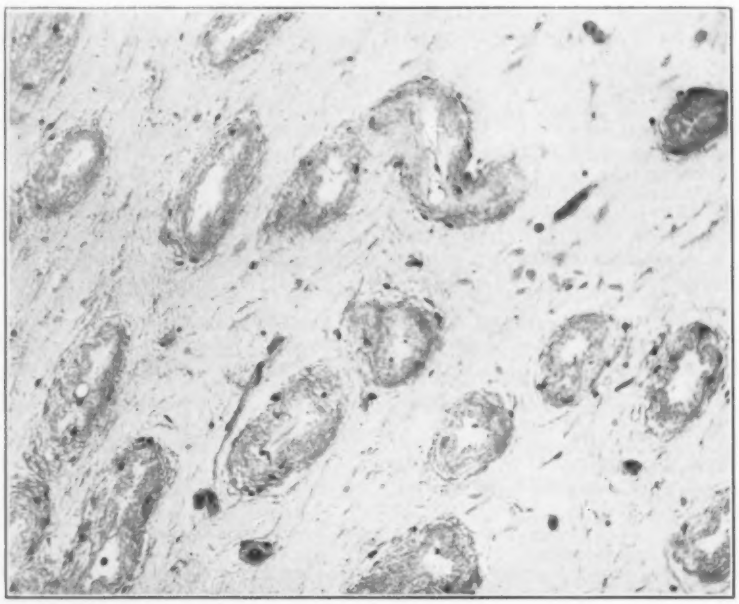

Fig. 1.—Photomicrograph (× 135) of testicular biopsy specimen of patient H. D. Note the complete hyalinization of the seminiferous tubules and absence of Leydig cells. Both testes revealed the same pattern. An entirely similar picture was seen in the bilateral testicular biopsy specimens of patients M. A. and E. H.

*Radio-iodine studies were performed by Dr. Kenneth Corrigan, Harper Hospital, Detroit.

receiving ACTH, revealed subnormal values. Depressed radio-iodine uptake has been repeatedly observed in patients receiving ACTH and cortisone[4], and thus ACTH therapy may have been responsible for the low values observed in patients M. A. and E. H. Neither patient developed signs or symptoms of hypothyroidism during therapy.

RESPONSE TO PROLONGED MAINTENANCE THERAPY. Two patients, M. A. and H. D., have been closely observed for two and one-half years, during which time they have received ACTH, chorionic gonadotrophin and testosterone. Both patients were initially treated with 25 to 50 units of aqueous ACTH daily, intramuscularly. This resulted in a marked increase in strength, increase in appetite, improvement in mental outlook, and an increase in weight of 10 to 20 pounds, but no growth of pubic, axillary and body hair, or return of potency. Increased pigmentation of the exposed areas of the skin, similar to "tanning," but unrelated to exposure to the sun, and darkening of the areolae of the nipples were first noted during the third month of treatment in both patients.

Chorionic gonadotrophin, 2,000 to 5,000 units intramuscularly daily for 48 days, was administered to both patients during the first 2 months of ACTH therapy to determine if the testis was capable of responding to stimulation; no effect was noted in either patient. After 3 to 4 months of ACTH therapy, treatment with testosterone propionate, 25 mg. intramuscularly daily, was initiated, and within 2 weeks return of normal potency was reported. After 2 to 4 months of combined ACTH and testerone therapy, growth of beard and pubic and axillary hair was first observed.

After the first 6 to 8 months of therapy, ACTH was withdrawn to see if improvement could be maintained on testosterone alone. Four weeks after stopping ACTH, and while still receiving testosterone propionate, 25 mg. daily, patient M. A. complained of weakness, anorexia, and leg cramps; these symptoms promptly disappeared with reinstitution of ACTH treatment. In patient H. D., ACTH therapy was stopped for 6 months, during which time testosterone propionate was continued in the amount of 25 mg., intramuscularly, every other day. No apparent change was noted for 2 months, and then weakness, anorexia, leg cramps and mental depression gradually returned. An 8-pound weight loss occurred during the last month. The resumption of ACTH therapy resulted in restoration of strength, well-being, appetite and weight.

Subsequently both patients have been well maintained on an average daily dose of 10 units of ACTH in either aqueous or long-acting vehicles. It should be emphasized that although ACTH and testosterone therapy corrected the adrenal cortical and androgen deficiency, no features of hypothyroidism developed. A more detailed account of the patients' courses, with charts correlating therapy, 17-ketosteroid excretion and clinical response, is presented in another report.[9].

Discussion. At least two mechanisms can be postulated to explain the association of testicular and adrenal cortical deficiency with preservation of thyroid function observed in these cases of hypopituitarism: first, SELECTIVE PITUITARY FAILURE, resulting in lack of gonadotrophin and corticotrophin secretion with preservation of adequate thyrotrophin secretion; and second, PARTIAL PANHYPOPITUITARISM, resulting in uniform depression in secretion of all trophic hormones to a level insufficient for one or more target organs, yet still adequate for the remainder. The studies indicated that

the failure of gonadotrophin and corticotrophin secretion was relatively complete. If a comparable depression in thyrotrophin secretion had been present, it seems unlikely that adequate thyroid function could have been maintained.

In the natural development of panhypopituitarism, the manifestations of failure of each of the target organs may make their appearance at different times, and furthermore, the signs of failure of one target organ may obscure the features of deficient function of the others. Time would not appear to be a factor in our cases, since the disease had been present for many years in each patient. In patient H. D., complete lack of pubic, axillary and body hair and the complaint of complete impotence were recorded in a hospital record 23 years ago. The possibility that the appearance of hypothyroidism was obscured by the combined adrenal cortical and testicular deficiency also seems unlikely, since correction of these deficiencies with ACTH and testosterone (but not thyroid substance) did not precipitate hypothyroidism. Although no final conclusions can be made until sensitive and accurate methods are available for assay of thyrotrophin and adrenocorticotrophin, we feel that the evidence cited above favors selective pituitary failure, rather than panhypopituitarism, as the basis of this syndrome.

It is of interest that the adrenal cortex was capable of adequately responding to stimulation with ACTH after more than 20 years of inactivity, whereas irreversible testicular damage had occurred as evidenced by the biopsy findings of complete hyalinization and the lack of response to large doses of chorionic gonadotrophin. It can be expected that although ACTH will correct the adrenal cortical deficiency, testosterone substitution therapy, rather than stimulation with gonadotrophins, will be necessary to correct the androgen deficiency in most long-standing cases of hypopituitarism.

The complete hyalinization of the testis present in our cases might suggest intrinsic testicular degeneration; however, in studies of testicular changes associated with destructive lesions of the pituitary, severe hyalinization of the basement membrane and peritubular fibrosis were frequent findings[5,7]. We feel that the complete hyalinization present in our cases reflects the severe degree and long duration of gonadotrophin failure.

Albright and Elrick[1], as mentioned previously, proposed a theoretical classification of selective pituitary failure based on alterations in function of pituitary basophils and acidophils. Since all of our patients are still alive, no conclusions can be made as to correlation of function and cytological alterations. Studies in animals suggest that each pituitary hormone is derived from a specific cell type. *Alpha* and *epsilon* types of acidophils have been delineated[13], and are believed to secrete growth and lactogenic hormones, respectively[10]. Three kinds of basophils, *beta, gamma* and *delta* types, have been differentiated[2,13]. Delta cells have been implicated as the source of gonadotrophins[2], and beta cells appear to be the source of thyrotrophin[12]. The origin of adrenocorticotrophin remains unsettled although the majority of evidence favors some type of basophil as its source[14]. If these animal studies are applicable to man, the findings in our patients may eventually be explained by failure of function of all types of basophils, except the "beta" cell.

Summary. SELECTIVE PITUITARY FAILURE is defined as deficient secretion of one or more, but not all, anterior pituitary trophic hormones, as contrasted with PANHYPOPITUITARISM in which there is uniform depression in

secretion of all pituitary trophic hormones. This report describes a type of selective pituitary failure observed in 4 men in whom failure of gonadotrophin and corticotrophin secretion was associated with evidence of intact thyrotrophin secretion. Deficient gonadotrophin secretion was manifested by clinical evidence of marked hypogonadism, biopsy evidence of testicular atrophy, and laboratory evidence of low urinary gonadotrophin excretion. Deficient corticotrophin secretion was demonstrated by clinical and laboratory evidence of adrenal cortical insufficiency which responded in an initially delayed but eventually satisfactory manner to ACTH therapy. Adequate thyrotrophin secretion was manifested by clinical and laboratory evidence of normal thyroid function. The duration of the disease varied from 6 to 24 years, yet each patient responded adequately to ACTH. Irreversible testicular damage, however, prevented a response to large doses of chorionic gonadotrophin, necessitating substitution therapy with testosterone.

ACKNOWLEDGMENT.: We wish to thank Dr. Warren O. Nelson for his help in interpreting the testicular biopsies.

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LIVER BIOPSY IN RHEUMATOID ARTHRITIS

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It is a matter of common knowledge that rheumatoid arthritis is not just a disease of joints, but rather a systemic malady, associated with an involvement of visceral organs. Most striking is the involvement of the heart. Amyloid degeneration is another example. The liver is also mentioned as an organ undergoing pathological changes in rheumatoid arthritis. Baggenstoss and Rosenberg[2] reported the following anatomic changes in the liver of their patients with rheumatoid arthritis who came to necropsy: gross hypertrophy and atrophy, chronic passive congestion, fatty changes, atrophy of the cells about central veins, central necrosis and the serous hepatitis of Rössle and Eppinger. At this point it is of some interest to recall the original observation by Hench[7,8], recording an improvement in the rheumatic state with the advent of liver disease and jaundice.

Several investigators have reported functional hepatic impairment in this disease. Thus Rawls, Weiss and Collins[13] demonstrated abnormal results of the azorubin S, hippuric acid, bilirubin excretion and galactose tolerance tests in many patients with rheumatoid arthritis. Carter and Maclagen[3] reported positive cephalin cholesterol flocculation and thymol turbidity tests. Pemberton and Foster[11] observed a slower return of the blood sugar level to the fasting figure following the oral administration of glucose in these patients than in normal subjects. This has been confirmed many times by other authors. Flynn and Irish[6] demonstrated similar findings after the intravenous injection of glucose and noted that the alteration thus could not be explained on the basis of gastrointestinal dysfunction. They also felt that differences in the renal threshold of glucose did not explain the altered glucose tolerance either, since approximately the same amount of glucose was lost in the urine of normal controls as in patients with rheumatoid arthritis. The authors concluded that the abnormal glucose tolerance was explainable on the basis of "an altered threshold of the hepatic homeostatis control of the blood sugar." However, they admitted that "additional studies must be done to determine whether this derangement emanates directly from extra hepatic influences". There were other studies on this subject, such as those of Hepburn, Warter and Rosenstein[9], Davis[5] , and Perlman and Kaufman[12], among other features including the study of electrophoretic distribution of proteins in serum, plasma, and synovial fluid.

A discordant note is sounded by Archer[1] who points out that "inasmuch as these investigators of liver function in arthritis apparently have not considered the possibility that many of the agents employed in the treatment of rheumatoid arthritis are hepatotoxic in nature, it is quite reasonable to believe that the results of their liver function tests may have been influenced by therapy". Archer found that when serial cephalin cholesterol flocculation

and thymol turbidity tests were done in cases of nonspecific arthritis during therapy with gold salts and other potentially hepatotoxic agents, the liver function tests, originally negative, sometimes became positive. In his own study several liver function tests (cholesterol flocculation, thymol turbidity and serum proteins) were carried out prior to the institution of any therapy. The cephalin cholesterol flocculation and thymol turbidity tests were consistently negative in all patients, contrary to the earlier findings of Carter and Maclagen[3]. The total serum protein and the serum albumin were also found to be normal, although there was a tendency toward the elevation of the serum globulin, resulting in a lowering of the average A/G ratio. Archer stresses the fact that "the lowering of the A/G ratio in nonspecific arthritis is not the result of a diminished albumin and a correspondingly elevated globulin, as seen in parenchymatous disease of the liver, but is the result of an elevated globulin alone". Hyperglobulinemia *per se*, as he correctly argues, is not necessarily an indication of liver damage, inasmuch as this biochemical change is present in a number of conditions in which there may be no hepatic disease.

It seems to us that the criticism leveled by Archer against the previous investigations of liver function in patients with rheumatoid arthritis, equally holds in the case of the pathological report by Baggenstoss and Rosenberg[2]. This study represents exclusively necropsy material and thus carries with it all the limitations that apply in such circumstances to the evaluation of exclusively necropsy data. In a subsequent communication[14] reporting an analysis of the causes of death in their patients with rheumatoid arthritis, these authors stated that the deaths could be listed under three headings: (1) those which seemingly resulted from the rheumatoid arthritis itself; (2) those which were related to the treatment of the arthritis and (3) those from causes unrelated to the arthritis or its treatment. In the latter category were encountered such conditions as rheumatic heart disease, pulmonary diseases (pneumonia, chronic suppuration, pulmonary embolism, fat embolism and massive collapse), renal lesions (pyelonephritis and oliguria, fatal amyloid degeneration), prolonged diarrheas of unknown origin and carcinoma. These conditions introduce imponderable factors potentially capable of producing liver damage on their own account.

We have been interested in the study of aspiration liver biopsies in patients both with "primary" hepatic and "nonhepatic" diseases[4,10]. The present report comprises a group of patients with rheumatoid arthritis.

Case Material. The series consisted of 17 patients. All patients were males. The ages varied from 26 to 59. All patients had rheumatoid arthritis involving the peripheral joints or the spine (Marie-Strümpell type) or both. One patient (J. N.) met the criteria of Reiter's syndrome. The duration of the disease varied from 1 to 396 months.

Methods. The liver function tests consisted of the following determinations: serum bilirubin, cephalin cholesterol flocculation, thymol turbidity, serum proteins (albumin, globulin and gamma globulin fractions), bromsulfalein dye excretion, alkaline phosphatase and plasma prothrombin concentration. In a few patients some of the above mentioned tests were inadvertently omitted. Biopsy specimens of the liver were obtained by Vim-Silverman needle, using the intercostal approach. The specimens were fixed immediately in alcoholic 10% formalin and, after the usual tissue mat imbedding, they were cut at 6 microns and stained with hematoxylin and eosin; in addition, Wilder and periodic acid leuco-fuchsin stains were prepared in some instances.

Results. Serum globulin was increased in 9 patients and gamma globulins in 11 patients. As to other tests, positive results, with few exceptions, were conspicuous by their absence. Thus in

TABLE 1.—SALIENT CLINICAL AND LIVER FUNCTION DATA IN 17 PATIENTS WITH ARTHRITIS STUDIED BY LIVER BIOPSY

Patient's name	*Age*	*Diagnosis*	*Duration of illness in months*	*Sedimentation rate (Westergren) mm. in 1 hr.*	*Serum bilirubin mg./100 cc.*	*Cephalin cholesterol flocculation (48 hrs.)*	*Thymol turbidity (units)*	*Serum proteins gm./100 cc.*			*Bromsulfalein retention in 45 min. (5 mg./kg. dose)*	*Alkaline phosphatase (activity)*	*Plasma prothrombin "time" (% of normal control)*
								Albumin	*Globulin*	*Gamma globulin*			
E. A.	58	rheumatoid arthritis	60		0.25	++++	9	3.9	3.3	1.5	0	1.7	100
O. N.	28	rheumatoid arthritis	3	83	0.4		5	4.3	2.6	1.0	3	3.4	100
H. B.	45	rheumatoid spondylitis	84	47	0.25	−	4	4.2	2.7	0.96	0	4.3	100
J. J.	28	rheumatoid spondylitis	24	75	0.25	±	4	3.9	2.4	1.44		2.6	93
P. W.	55	rheumatoid spondylitis	312	90	0.5	−	3	5.1	2.2	1.2	0		100
A. B.	52	rheumatoid arthritis	1	62	0.5	++++	20	4.0	3.7	2.16	3	3.2	93
E. McC.	29	rheumatoid arthritis	180	94	0.25	−		4.1	3.3	1.98			60
M. A.	38	rheumatoid arthritis	12	85	0.35	++	7	4.5	2.8	1.56	0	1	100
R. G.	26	rheumatoid arthritis and spondylitis	60	102	0.25	++	5	4.0	4.1	2.64		2.4	87
E. C.	59	rheumatoid arthritis	396	40	0.15	−	6	5.3	2.4	1.14	2	3.0	93
D. W.	56	rheumatoid arthritis	48	70	0.25	+	13	4.9	3.2	1.86	0	1.6	100
J. N.	28	Reiter's syndrome	72	65	0.4	+	4	4.5	3.4	1.02	2	2.0	100
T. M.	50	rheumatoid arthritis	60	71	0.35	+	4	4.7	3.0		1.5	1.5	100
W. F.	33	rheumatoid spondylitis	84	77	0.1	+		4.9	2.9		2		100
G. M.	38	rheumatoid arthritis	144	103	0.25	−	3	4.8	2.50	0.48	1	2.0	100
L. M.	27	rheumatoid arthritis and spondylitis	120		0.5	−	3	5.3	2.0	0.42	0	1.4	100
R. E.	28	rheumatoid	96	97	0.2	−	6	4.7	3.6		1	2.0	94

only 2 patients was the cephalin cholesterol flocculation test positive. In one of these patients (E.A.) the liver biopsy was normal. In another (A.B.) there was a slight fatty infiltration of the liver. In the latter case thymol turbidity was also elevated to 20 units. Serum albumin was slightly decreased in 2 patients and prothrombin concentration was decreased in another; in all 3 the biopsies were normal (See Table 1).

Liver biopsies showed slight fatty infiltration in 2 patients (H.B. and A.B.) and moderate fatty infiltration in another (J.N.). In one patient (R.E.) the small round cells in the portal triads were somewhat more numerous than usual. In still another patient (O.N.) the changes in the liver parenchyma were interpreted as indicating slight degenerative alterations with evidence of recovery. In the remaining 12 patients the biopsies were within normal limits, with slight and insignificant variations such as slight prominence of Kupffer-Stern cells and some coarsening of the reticulum fibers.

Comment. As is frequently the case, here also there was no correlation between the results of liver function tests and the anatomic findings. Thus in one patient (E.A.) with 4+ cephalin cholesterol flocculation test, the liver histology was surprisingly within normal limits. In another patient with 4+ cephalin cholesterol flocculation tests and the thymol turbidity of 20 units there was only mild fatty infiltration present. In both patients (E.A. and J. J.) with slightly decreased plasma albumin, the liver biopsies were entirely within normal limits. In one patient (E. McC.) low prothrombin time values were found in the face of normal liver biopsy.

A high incidence of elevated globulin and gamma globulin will be noted. However, it must be emphasized that these abnormal values were not necessarily associated with hypoalbuminemia, and thus probably did not reflect a state of abnormal liver function, but rather could be considered as being in the order of biochemical changes frequently seen in a number of different pathologic states, including rheumatoid arthritis. Thus we can readily see that the liver function, at least as reflected in the tests herein employed, can well be expected to be normal. In this respect we agree with Archer[1].

As to the anatomic state of the liver, we will note that biopsies were normal in most patients and that in only 4 out of 17 were there any alterations of note, such as slight to moderate fatty infiltration and evidence of the healing of a degenerative process. In a personal communication Dr. Gall informs us that his observations were in keeping with ours. He writes as follows: "A series of approximately 20 cases has been collected. . . . The findings were entirely nonspecific. In one instance there was severe amyloid disease. In another there were histologic changes of viral hepatitis. In the bulk of the remainder no diagnostic abnormalities were encountered, although there were varying amounts of liver cell fat and occasional foci of individual cell necrosis".

Summary. The present study was undertaken for the purpose of investigating the status of the liver, functional and anatomic, in patients with rheumatoid arthritis. A series of 17 patients were thus studied by performing liver aspiration biopsies and correlating anatomical material thus obtained with the results of a battery of hepatic function tests.

As a result of this study we are led to conclude that the functional capacity of the liver in rheumatoid arthritis, as demonstrated by the tests herein employed, is hardly affected at all or is

affected only to a very slight extent, and that pathologic changes in the liver in this condition are encountered only occasionally even in instances of the disease (rheumatoid arthritis) of long standing. The few changes found are nonspecific and anything but striking.

The literature on the subject is briefly reviewed.

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METASTATIC CARCINOMA OF THE ADRENAL

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Relatively few studies of large necropsy series of tumor metastases have appeared in recent literature. Exceptions include the study of 500 cases of cancer reported by Willis[11], and the 1000 cases of carcinoma studied by Abrams *et al.*[1]. Both studies demonstrated an exceptionally high incidence of adrenal involvement: 10% of the carcinomas reported by Willis and 27% of the cases reported by Abrams *et al.*, showed such involvement. The carcinomas which have metastasized to the adrenals have most frequently originated in either the lung or breast. Adrenal involvement has occurred in 14 to 44% of the patients with lung carcinoma[1,2,6,9,11] and in 20 to 53.9% of the patients with breast carcinoma[1,2,10,11].

Since a review of the Quarterly Cumulative Index Medicus failed to reveal a single study limited to metastatic carcinoma of the adrenals during the past 30 years, the authors made such a study at the Los Angeles County Hospital.

Method and Materials. Protocols from 19,700 consecutive necropsies previously reviewed in a study of metastatic carcinoma of the spleen[7] were again reviewed with reference to metastatic carcinoma of the adrenals. Two hundred and forty-four instances of metastatic carcinoma of the adrenal were found, of which 171 were recorded as having been histologically proved. Fifty-five of those were rejected: 51 because slides were not available for study, and 4 because of failure to demonstrate metastases. The remaining group of 116 histologically proved adrenal metastases were studied and observations made as to location (with relation to vessels, cortex, and medulla) and size of the secondary tumors. Microscopic sections usually consisted of a single slide stained with hematoxylin and eosin. The following criteria were used in assessing vascular invasion: presence of tumor cells in association with thrombi or numerous red cells, in capillary-sized vessels were considered evidence of capillary metastasis. Clumps of tumor cells within the adrenal but exterior to capillaries or other blood vessels were assumed to be in lymphatics or tissue spaces. The characteristic histologic features of arteries and veins made recognition of tumor emboli within them relatively easy.

Adrenals containing metastatic carcinoma were classified grossly into three groups: normal to only slightly enlarged, (weighing less than 10 gm. or containing a tumor nodule less than 2.5 cm. in diameter); moderately enlarged, (weighing 10 to 30 gm. or containing a nodule 2.5 to 5 cm. in diameter); and markedly enlarged, (weighing over 30 gm. or containing a tumor over 5 cm. in diameter).

Results. The finding of 244 metastatic carcinomas of the adrenal in a total of 2833 carcinomas is an incidence of 8.6%. This over-all incidence approximates that reported by Willis (10%) but differs from the incidence obtained by Abrams *et al.*, (27%). The frequency of metastases to the adrenal from the epithelial tumors in our ser-

ies is compared with that obtained by these authors in Table 1.

GROSS STUDIES. Descriptions of the adrenals with metastases were available for review in 98 of the histologically proved group. Of these, the adrenals were either normal in size or slightly enlarged in 69, moderately enlarged in 18, and markedly enlarged in 11. In the latter group the adrenal weights varied from 32 to 320 gm. The preponderance of normal-sized glands was a striking feature of the gross descriptions. Not infrequently, adrenal metastases were not seen externally but were revealed only by sectioning the adrenal or by microscopic examination.

Mention was made as to which adrenal was involved in 99 of the microscopically proved metastases. Tumors were bilateral in 64 and unilateral in 35, with involvement of the right adrenal in 19 and the left in 16. Willis also noted the tendency of adrenal metastases to be bilateral, with a slightly greater frequency of involvement of the right as compared to the left adrenal in those with unilateral metastases.

HISTOLOGIC STUDIES. Using the criteria of vascular invasion stated above, there were only 8 instances of cortical capillary involvement and an equal number with capsular arteriolar involvement. Much more frequent

TABLE 1.—METASTATIC CARCINOMA OF THE ADRENAL

	Willis[11]			Abrams, Spiro, and Goldstein[1]			Bullock and Hirst*		
Number of carcinomas reported	420			1000			2833		
Number with adrenal metastasis	42			270			244		
		Adrenal involvement			*Adrenal involvement*			*Adrenal involvement*	
Primary sites	*No. cases*	*No.*	*%*	*No. cases*	*No.*	*%*	*No. cases*	*No.*	*%*
Lung (bronchus)	27	12	44.4	160	57	35.6	397	114	28.7
Breast	45	9	20	167	90	53.9	186	24	12.8
Stomach	85	4	4.7	119	25	21.0	401	19	4.7
Colon and Rectum	65		3	205	28	13.6	355	15	4.2
Pancreas	11	1	9	32	6	19	175	14	8.0
Kidney	10	2	20	34	8	24	70	13	18.5
Melanoma							32	10	31.2
Uterus	30								
Cervix							226	8	3.5
Corpus							32	2	6.2
Thyroid	6	2	33.3				9		
Others or Undetermined	18	3	16.6				45	5	11.1
Prostate	15	1	6.6				208	4	1.4
Gallbladder							83	3	3.6
Esophagus	17						35	3	8.5
Pharynx							32	2	6.2
Ovary	9			64	11	17	79	2	2.5
Parotid							8	1	12.5
Larynx							50	1	2.0
Penis							8	1	12.5
Bladder							135	1	0.7
Sinuses (maxillary, etc.)							12	1	8.3
Testicle							14	7	7.1
Epidermoid Carcinoma (head and neck)	64	5	7.8						

* Present Series

with 38 instances, was invasion of the large medullary veins. Such involvement was usually noted in association with extensive metastatic involvement of both cortex and medulla. Once the tumor has reached the adrenal, it appeared that spread was primarily by lymphatics or tissue spaces and that venous spread, when it occurred, was a late phenomenon.

Metastases were further divided into capsular, cortical, and medullary groups. It was possible to determine localization in 116 cases showing histologic evidence of adrenal metastases. The largest group, 58 cases, showed involvement of both cortex and medulla to approximately the same extent. In 36 instances the metastatic tumor was predominantly medullary and in only 17 was it predominantly cortical. In 2 the metastases were limited to the capsule. Assuming that larger aggregates of tumor suggest older lesions, it appears that the majority of metastases reach the medulla first. This finding is in agreement with a similar observation by Willis[11].

Discussion. In our series, lung carcinoma was responsible for over four times as many adrenal metastases as any other tumor. The percentage incidence of adrenal metastases from a primary lung carcinoma (28%) was not as high as the frequency of adrenal involvement from malignant melanoma (31.2%). These data suggest that if malignant melanoma were as frequent as bronchogenic carcinoma, that it would equal or exceed it in the number of adrenal metastases. Both of these tumors have a tendency to widespread metastasis. Other primary carcinomas that frequently spread to the adrenals arose in the breast, stomach, colon and rectum, and pancreas. The overwhelming majority of adrenal metastases occurred from primary tumors which had metastasized to three or more additional organs, suggesting that adrenal involvement is part of a generalized tumor dissemination. Although bronchogenic carcinomas have been known to involve selectively the adrenals to the exclusion of other metastases[2], no such instance was found in our histologically proved group. The predominance of metastases of small size suggests that adrenal involvement probably occurs late in the course of tumor dissemination.

Of the three channels by which carcinomas are likely to spread to the adrenals, namely, arteries, lymphatics, and veins, blood vessels would seem to be the most logical channel, for the primary tumor is usually located at a distant site and the adrenals possess certain anatomic peculiarities which may account for their susceptibility to metastases. First, their profuse arterial supply from three different sources would theoretically expose this organ to a relatively large number of tumor emboli. Second, the adrenal arteries divide into minute vessels before they enter the cortex to form numerous capillaries which subsequently join to form large venous channels within the medulla. A parenchymal blood flow to the adrenal supplied chiefly by capillary-size vessels may be significant. Coman *et al.*[4] injected rabbits intra-arterially with cell suspensions of Brown-Pearce tumor and found the frequency of tumor growth was proportional to the number of tumor emboli reaching the capillaries of a given organ. A high incidence of adrenal metastases was found in their studies. Venous spread, which implies obstruction by tumor and retrograde propagation along the adrenal veins, is probably an infrequent cause of adrenal metastases.

Studies of testicular tumors by Dixon and Moore[5] support the contention that lymphatics may be an important

mode of spread to the adrenals. They noted four times as many metastases to the left as to the right adrenal and relate this distribution to the anatomic arrangement of the lymphatics. The lymphatics of the left testicle drain into nodes about the left renal vein while those from the right testicle drain into the periaortic chain of lymph nodes. Our histologic studies support the concept that intra-adrenal spread is primarily by lymphatics or tissue spaces, but did not establish the mode of entry into the adrenals.

Conclusions. 1. Two hundred and forty-four cases of metastatic carcinoma of the adrenals were encountered among 2833 carcinomas in 19,700 consecutive necropsies.

2. In terms of decreasing numerical frequency, the tumors which most often metastasized to the adrenals had their origin in the lung, breast, stomach, colon and rectum, and pancreas.

3. Adrenal metastases were usually bilateral small tumors, which apparently occurred late in the dissemination of carcinoma.

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CLINICAL AND LABORATORY STUDIES OF INFECTIONS DUE TO *PSEUDOMONAS AERUGINOSA* AND PSEUDOMONAS SPECIES*

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Infections due to pseudomonas species have not been accorded the emphasis given to those caused by *Pseudomonas aeruginosa*[1,2,6]. The laboratory and clinical studies which follow are presented to emphasize that there is a distinct difference in the susceptibilities of these organisms to antibiotics and to outline the optimal treatment against infections due to both pseudomonas species and *Ps. aeruginosa*.

Materials and Methods. The sensitivity to antibiotics of 57 strains of *Pseudomonas aeruginosa* and 38 strains of pseudomonas species was determined by the tube dilution method[5]. All strains of bacteria were isolated by the clinical bacteriology laboratory from patients with infections on the wards of the Milwaukee County General Hospital. Identification of the organisms was done in the usual manner by observation of colony formation, pigment production, and sugar fermentation reactions. *Ps. aeruginosa* was differentiated from pseudomonas species by the presence or absence of detectable dye formation on blood agar plates. Strains that had all the characteristics of *Ps. aeruginosa* except that of detectable dye formation were designated as pseudomonas species. The majority of patients from whom the organisms were isolated were observed by at least one of us and insofar as was possible their treatment was determined by *in vitro* studies. The hospital charts were then studied for objective evidence of correlations between the *in vitro* studies and clinical results. Particular note was made of instances in which infections due to pseudomonas species followed therapy for a *Ps. aeruginosa* infection. Five of the best-studied and most informative cases were selected for presentation as examples of our over-all experience in the treatment of infections due to *Ps. aeruginosa* and pseudomonas species.

Results. 1) The results of the sensitivity tests performed on 57 strains of *Ps. aeruginosa* and 38 strains of pseudomonas species are shown on Table 1. Every strain of *Ps. aeruginosa* was sensitive to the action of polymyxin B. Oxytetracycline was the next most effective drug against this organism. When these drugs were combined an additive and in certain cases a potentiating effect was obtained (Table 1). Aureomycin, chloramphenicol, streptomycin, and neomycin were not as effective in inhibiting *Ps. aeruginosa* as were polymyxin B and oxytetracycline (Table 1). The results of the tests performed with the strains of pseudomonas species were markedly different (Table 2). Neomycin and chloramphenicol were the agents to which the least number of strains were resistant**.

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**Due to the high blood concentrations obtained with chloramphenicol organisms inhibited by a concentration of 25 μg/ml. of this agent usually respond clinically to its administration.

TABLE 1.—THE COMPARATIVE SENSITIVITIES OF 57 STRAINS OF PSEUDOMONAS AERUGINOSA TO 6 ANTIBIOTICS AND THE COMBINATION OF OXYTETRACYCLINE AND POLYMYXIN B

Inhibitory concentrations in μg/cc.	*Polymyxin B*	*Oxytetracycline*	*Polymyxin B and Oxytetracycline*	*Aureomycin*	*Neomycin*	*Chloramphenicol*	*Streptomycin*
<.38	24*, 42		42		24		
.38			12, 21, 37, 42B				18, 24, 39
.75	6, 10, 14, 15, 18, 19, 21, 31, 35, 37, 38, 39, 41, 6A**, 9A, 42A, 42B, 50, 51		15, 20, 23, 25, 26, 27, 30, 31, 36, 38, 39, 42A, 48, 58, 59		28, 42		
1.5	4, 5, 7, 8, 12, 13, 17, 20, 22, 23, 26, 27, 30, 36, 40, 25, 47, 52, 53, 55, 56, 57, 58, 59	1, 19, 42	2, 3, 4, 5, 6, 22, 35, 43, 47, 54	24	18, 27		
3	1, 2, 11, 26, 29, 32, 34, 43, 45, 48, 54			5, 19, 42	10, 12, 21, 31, 37, 6A, 51		6
6	3, 9, 33, 49	6, 7, 8, 9, 10, 13, 20, 25, 30, 32, 35, 36, 41, 6A, 9A, 45, 47, 50, 51		1, 6, 15, 30	5, 6, 9, 15, 16, 19, 20, 23, 26, 33, 41, 42A, 50, 55, 57	28	9, 19, 27, 35
12		16, 23, 27, 29, 31, 33, 37, 38, 39, 43, 42A, 42B, 48, 49, 53, 56, 57		3, 9, 11, 14, 17, 20, 22, 26, 31, 32, 36, 40, 43, 6A, 44, 47, 52	1, 7, 8, 17, 22, 25, 30, 32, 34, 36, 38, 40, 9A, 42B, 45, 47, 49, 54		25, 26, 32, 9A, 55
25		34, 58		2, 4, 8, 12, 13, 18, 21, 25, 27, 29, 34, 35, 37, 38, 39, 41, 9A, 23, 45, 48, 49, 51, 53, 56, 58, 59	2, 13, 14, 39, 48, 52, 53, 56, 59		10, 23, 33, 34, 6A, 49
50		54, 55		7, 10, 16, 28, 33, 42A, 50, 54, 55, 57	3, 4, 11, 29, 43	19, 42	29, 43, 54
100						1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 22, 23, 25, 26, 29, 31, 33, 34, 35, 36, 37, 38, 39, 40, 41, 43, 6A, 9A, 42A, 45, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57	58
>100		28			58		1, 2, 3, 4, 5, 7, 8, 11, 12, 13, 14, 15, 16, 17, 20, 21, 22, 28, 30, 31, 36, 37, 38, 40, 41, 42, 42A, 42B, 45, 47, 48, 50, 51, 52, 53 56, 57, 59

* Each numb[illegible] a strain from a different patient.
** Multiple cultur[illegible] the same patient are numbered the same as the original culture but a letter is added.

TABLE 2.—THE COMPARATIVE SENSITIVITIES OF 38 STRAINS OF PSEUDOMONAS SPECIES TO 7 ANTIBIOTICS

Inhibitory concentrations in μg/cc.	*Polymyxin B*	*Oxytetracycline*	*Aureomycin*	*Neomycin*	*Chloramphenicol*	*Streptomycin*	*Penicillin*
<.38	2*	2	2				
.38				2, 3A			
.75	15	19	9, 22	8, 19, 21, 23A			
1.5	9, 19, 21, 23A*	3A, 9, 15, 21	3A, 21	9, 15		21	23
3	3A, 16	16, 22	15, 19	4, 11, 14, 24		19	
6	22	23A		5, 10, 17, 21B, 29	21, 24		
12			16, 23	1, 16, 20, 23, 25, 26, 27, 28, 30, 32	14, 22, 23, 29, 31		21
25			6, 8, 23A, 24	6, 12, 13, 18, 21A 31, 33	1, 2, 3, 4, 6, 12, 3A, 17, 19, 20, 25, 26, 27, 28, 30, 33, 34, 35	9	2
50		23	4, 5, 11, 13, 27	3, 7, 34, 35, 36	9, 13, 15, 36		3A, 14
100	23	6, 13, 14	10, 12, 14, 20, 21B, 25, 26, 28, 29, 32		7, 21A, 21B	12, 22	6, 8, 9, 19
>100	1, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 17, 21A, 21B, 25, 26, 27, 28, 29, 24, 30, 31, 32, 33, 34, 35, 36, 37, 38	1, 3, 4, 5, 7, 8, 10, 11, 12, 17, 18, 20, 21A, 21B, 25, 26, 27, 28, 29, 24, 30, 31, 32, 33, 34, 35, 36, 37, 38	1, 3, 7, 17, 18, 21A, 30, 31, 33, 34, 35, 36, 37, 38	22, 37, 38	5, 8, 10, 11, 16, 18, 23A, 32, 37, 38	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 3A, 13, 14, 15, 16, 17, 18, 20, 21A, 21B, 23, 23A, 25, 26, 27, 28, 29, 24, 30, 31, 32, 33, 34, 35, 36, 37, 38	1, 3, 4, 5, 7, 16, 11, 12, 13, 15, 16, 17, 18, 20, 21A, 21B, 22, 23A, 25, 26, 27, 28, 29, 24, 30, 31, 32, 33, 34 35, 36, 37, 38

* See footnotes on *TABLE 1.*

The majority of the strains were resistant to all other antibiotics but a few of them were sensitive to each agent. Thus, in a specific case, if treatment were to be given without the aid of *in vitro* studies, neomycin or chloramphenicol would be the drug of choice. However, laboratory studies might reveal the organisms to be more sensitive to any of the other antibiotics.

2) In only 21 of the 50 charts that were carefully studied was definitive objective evidence as to the result of therapy obtained. The results in these cases are shown in Table 3. These results are, in our opinion, representative of those in our entire experience, since we have found that treatment of *Ps. aeruginosa* infections with oxytetracycline or polymyxin B resulted in equal numbers of frank failures, cases of the emergence of infections due to pseudomonas species, and bacteriologic cures. In addition, an occasional case that did not respond to polymyxin B or oxytetracycline used alone was cured by the combination of these drugs.

TABLE 3.—THE RESULTS OF THERAPY IN 21 CASES OF INFECTIONS DUE TO *PSEUDOMONAS AERUGINOSA*

No. of cases	*No. of cases in which* Ps. aeruginosa *was replaced by pseudomonas species*	*No. of clinical and bacteriologic cures with oxytetracycline*	*No. of bacteriologic failures with oxytetracycline*	*No. of clinical and bacteriologic cures with Polymyxin B and oxytetracycline combined*
21	8	5	7	1

TABLE 4.—THE RESULTS OF SENSITIVITY TESTS ON BACTERIA ISOLATED FROM THE PATIENTS WHOSE CASES ARE REPORTED IN DETAIL

Species of bacteria and case number	*Aureo.**	*Chloro.*	*Terra.*	*Poly. B.*	*Terra. & Poly. B*	*Pen.*	*Strep.*	*Neo.*
Case 1								
Ps. aeruginosa	50**	100	6	12	3	>100	>100	12
Case 2								
Ps. aeruginosa	3	50	1.5	<.38	<.38	>100	>100	.75
Case 3								
Ps. aeruginosa	1.5	6	1.5	1.5		12	1.5	.75
Ps. species	>100	100	>100	>100		>100	>100	25
Case 4								
Proteus	25	12	100	>100		.75	1.5	6
Ps. aeruginosa	3	50	1.5	.75		>100	>100	1.5
M. pyogenes	12	100	>100	>100		>100	>100	.38
Case 5								
Proteus	>100	25	>100	>100		1.5	3	6
Ps. species	25	25	100	>100		100	>100	25

* Aureo.=Aureomycin
Chloro.=Chloramphenicol
Terra.=Oxytetracycline
Poly. B=Polymyxin B
Terra. & Poly. B=Oxytetracycline and polymyxin B
Pen.=Penicillin
Strep.=Streptomycin
Neo.=Neomycin

** The figures refer to the inhibitory concentrations of each antibiotic as expressed in micrograms per cubic centimeter

Case Reports. CASE 1. The patient was a 20-year old white unmarried woman who entered the hospital with a diagnosis of chronic pyelonephritis and a chief complaint of frank hematuria of one week's duration. Complete renal function studies and retrograde pyelograms previously had been normal. Physical examination revealed a temperature of 102.8° F. and right flank tenderness. Urinalysis revealed a specific gravity of 1.013, 4 plus albumin, 40 to 50 red blood cells per high power microscopic field, and 3 to 5 white blood cells per high power

microscopic field. Urine cultures grew *Ps. aeruginosa* and *Escherichia coli*. Antibiotic sensitivity tests showed the *Ps. aeruginosa* to be most sensitive to the combination of polymyxin B and oxytetracycline (Table 4). Oxytetracycline, 0.5 gm. by mouth every 6 hours, and polymyxin B, 50 mg. intramuscularly every 12 hours, were administered for 2 weeks with rapid clinical improvement and clearing of the urine. At the end of that time a urine culture grew coagulase positive *Micrococcus pyogenes* which was sensitive to chloramphenicol. After a 10-day course of chloramphenicol the patient was entirely asymptomatic and her urine was crystal clear. A urine culture just prior to discharge grew *E. coli*.

COMMENT. This case illustrates the eradication of *Ps. aeruginosa* from the urine by the simultaneous administration of oxytetracycline and polymyxin B. It also illustrates the futility of trying to sterilize the urine of patients with chronic pyelonephritis. The justification for initiating therapy in this case was the fever and hematuria. The *E. coli* isolated in the final culture was being well tolerated and was not an indication to subject the patient to further therapy.

CASE 2. The patient was a 54-year old white diabetic female who entered the hospital with complaints of backache and dysuria of several months' duration. Physical examination revealed a temperature that ranged from 100° F. to 104° F. and a grade II uterine prolapse with a cystourethrocele. Urinalysis revealed specific gravity of 1.010, one plus albumin, no sugar, and 150 to 200 cells per high power microscopic field. A urine culture grew *Ps. aeruginosa, E. coli* and *M. pyogenes*. The *Ps. aeruginosa* was sensitive to oxytetracycline and polymyxin B, and the *M. pyogenes* was most sensitive to aureomycin (Table 4). The patient was given 2 gm. per day of oxytetracycline for 2 weeks with clinical improvement. At the end of that time *Ps. aeruginosa* and *M. pyogenes* were again cultured from the urine. Fifty milligrams of polymyxin B were then administered intramuscularly twice daily for 13 days. During this time she had one episode of acute fever but her urine gradually cleared. At the end of this time *Ps. aeruginosa* was again cultured from her urine, but since she was afebrile, asymptomatic, and her urine was normal, she was discharged.

COMMENT. This case is illustrative of the fact that, in spite of apparent *in vitro* sensitivity to both oxytetracycline and polymyxin B, many infections due to *Ps. aeruginosa* do not respond to the administration of these agents. Since the patient was clinically well, we did not feel justified in continuing our attempt to sterilize her urine. If she has further difficulty, correction of the pelvic abnormalities would be attempted before definitive chemotherapy was administered.

CASE 3. The patient was a 75-year old white male who entered the hospital because of inability to void. Examination revealed benign prostatic hypertrophy and a temperature of 103° F. Urinalysis showed a specific gravity of 1.015, 4 plus albumin, and numerous red and white blood cells per high power microscopic field. A urine culture grew *Ps. aeruginosa* which was equally sensitive to oxytetracycline, aureomycin, streptomycin and polymyxin B (Table 4). Two grams of aureomycin were administered by mouth each day but the temperature continued to spike and a blood culture grew *Ps. aeruginosa*. Penicillin and streptomycin were then added to the aureomycin, and as soon as the patient seemed to respond, a suprapubic prostatectomy was done. Specific medication was then omitted and methenamine mendelate (Mandelamine) was given by mouth 3 times daily with continued improvement. Repeated urine cultures after the operation revealed pseudomonas species which were sensitive only to neomycin (Table 4). The patient was discharged without fever, without dysuria, and with his urine still containing pseudomonas species.

COMMENT. This case illustrates the emergence of pseudomonas species in a patient who was given intensive therapy for a *Ps. aeruginosa* infection. This strain was completely resistant to all antibiotics that are available for general use.

CASE 4. The patient was a 56-year old white female who had had subacute pyelonephritis for many years and who had had an infected left kidney removed 11 years before admission. Hospitalization had been advised because she was having almost daily

attacks of chills and fever. Physical examination revealed an obese woman who did not appear acutely ill. Temperature was 102.6° F., pulse was 86, respirations were 20 per minute, and blood pressure was 200/100. Laboratory studies were as follows: urine, specific gravity 1.010; one plus albumin; no red blood cells, and 7 to 8 white blood cells per high power microscopic field; blood, hemoglobin 97%; white blood cell count 7,000 with 90% polymorphonuclear leukocytes; nonprotein nitrogen concentration was 42 mg. per 100 cc. A urine culture grew proteus which was sensitive to penicillin and chloramphenicol[4]. (Table 4). Therapy with these agents was begun, and a urine culture drawn one week later grew *Ps. aeruginosa*. Polymyxin B and oxytetracycline were begun (Table 4). There was no marked change in the clinical condition of the patient, but the urine culture drawn just before the patient signed her release and left the hospital revealed proteus and coagulase positive *M. pyogenes*.

COMMENT. The mixed nature of the infection in patients with chronic or subacute pyelonephritis is illustrated by this case. The proteus was the predominant organism but when it was suppressed by the combination of penicillin and chloramphenicol, *Ps. aeruginosa* emerged as the infecting organism. When oxytetracycline and polymyxin B were administered, the *Ps. aeruginosa* lost its competitive advantage, and the proteus again was able to emerge to complete the cycle we have seen in numerous cases of chronic pyelonephritis in which therapy with antibiotics was attempted.

CASE 5. The patient was an 84-year old white woman who entered the Milwaukee County General Hospital with complaints of malaise and dysuria. Physical examination revealed temperature of 105° F., pulse 150 and irregular, emaciation, rales at the base of the left lung, and cardiac enlargement and irregularity. Laboratory studies revealed the following: blood, hemoglobin 94%; white blood count 27,000 with 94% polymorphonuclear leukocytes; nonprotein nitrogen concentration, 51 mg. per 100 cc.; urine, albumin 4 plus; 18 to 22 white blood cells per high power microscopic field; urine culture proteus.

COURSE: The patient was given general supportive therapy and the combination of penicillin and sulfisoxazole (Gantrisin). She became afebrile within 24 hours, but continued to appear acutely ill. On the third hospital day her temperature rose again to 105° F. and a blood culture grew pseudomonas species. Oxytetracycline was then administered, but a blood culture on the fifth hospital day again grew pseudomonas species. The sensitivity to antibiotics of the strains of proteus and pseudomonas species was determined and on the basis of the results, the intramuscular administration of 2 gm. per day of chloramphenicol was begun (Table 4). The patient seemed much improved and three blood cultures drawn during the 7 days that chloramphenicol was being given were sterile. The administration of 500,000 units of aqueous penicillin intramuscularly twice per day was begun when the chloramphenicol was discontinued. During this time three urine cultures grew pseudomonas species but the patient seemed to be improving. The penicillin was discontinued after 10 days; 24 hours later the patient had a chill, and her temperature rose to 103° F. A blood culture drawn at this time grew proteus. Ten million units of penicillin were administered intravenously and the patient seemed somewhat improved[3]. She suddenly died on the 33rd day after entering the hospital.

Postmortem examination revealed a large collection of creamy pus in the left ureter and a large perinephric abscess. Proteus and pseudomonas species were cultured from these lesions.

COMMENT. This case is an example of the type of response we have encountered when infections that clearly demanded surgical intervention were treated with antibiotics. The proteus was sensitive to penicillin and chloramphenicol and the pseudomonas species was sensitive to chloramphenicol. Thus, when penicillin was given, the pseudomonas species emerged as the dominant pathogen and was repeatedly found in the blood stream. When the penicillin was discontinued, the proteus regained dominance and was the organism isolated from the blood. While these interactions between the antibiotics and two species of bacteria were going on, the patient

died without the benefit of the surgical intervention that she so urgently needed.

Discussion. These *in vitro* studies and clinical experiences indicate that the combination of polymyxin B and oxytetracycline should be administered to patients with treatable infections due to *Ps. aeruginosa*. Polymyxin B has an advantage over oxytetracycline because weight for weight it is more effective and is bactericidal in action. These advantages are counteracted by the larger doses of oxytetracycline that may be administered safely (the average dose of polymyxin B is 150 mg. per day and the average dose of oxytetracycline is 2 gm. per day). The main consideration in the treatment of infections due to *Ps. aeruginosa* is whether or not the infection is of a type that responds to any chemotherapy. We have found that if therapy with antibiotics is attempted against infections such as chronic draining sinuses, chronic otitis media, or chronic pyelonephritis, the *Ps. aeruginosa* is often suppressed, but that more virulent or more resistant bacteria such as proteus or pseudomonas species emerge as the prominent pathogen of the infection. The specific infections due to *Ps. aeruginosa* in which polymyxin B and oxytetracycline have been of therapeutic aid in our experience include meningitis (we have administered 10 mg. of polymyxin B intrathecally once per day), certain pulmonary infections, acute septicemia, acute pyelonephritis, and secondary infections over burned areas. The treatment of *Ps. aeruginosa* infections that cover large burned areas with the local administration of polymyxin B in a concentration of one milligram per milliliter has been gratifying and has allowed early preparation for skin grafting.

The wide variation in sensitivity to antibiotics exhibited by various strains of pseudomonas species makes it mandatory to determine the *in vitro* sensitivity of a particular strain that is causing a serious infection. In our experience chloramphenicol has cured a few infections due to this organism, but the great majority of cases have not been affected by chemotherapy with any of the antibiotics. In several instances we have continued to isolate pseudomonas species from the blood and urine of patients in spite of therapy with sulfisoxazole, penicillin, streptomycin, aureomycin, oxytetracycline, chloramphenicol and polymyxin B.

Since very few of the strains of pseudomonas species respond to either polymyxin B or oxytetracycline, it is of clinical importance that the laboratory clearly indicate whether or not pseudomonas organisms isolated from patients do or do not form dye on blood agar plates. If the organisms are true *Ps. aeruginosa,* the clinician will know that the infection has a fair chance of responding to polymyxin B and oxytetracycline. If no dye is formed by the organism, there is much less of a chance that the infection will respond to chemotherapy and this knowledge will allow the clinician a realistic viewpoint of the situation and possibly save the patient much unnecessary medication.

The close correlation between the results of the *in vitro* tests of the sensitivity of the organisms to antibiotics and clinical results should serve to emphasize the importance of laboratory control of the therapy of severe infections due not only to organisms of the pseudomonas group but in all severe bacterial infections (Table 4).

Summary and Conclusions. *In vitro* and clinical studies of the effectiveness of antibiotics against *Ps. aeruginosa* and pseudomonas species were presented in this report. Polymyxin B and oxytetra-

cycline were the most effective antibiotics against infections due to *Ps. aeruginosa*.

Antibiotics were not effective against the majority of strains of pseudomonas species, but chloramphenicol and neomycin appeared to be the best agents for use against these bacteria.

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URETHRAL APOPLEXY: AN EARLY SYMPTOM OF MALIGNANT HYPERTENSION

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In most instances of malignant hypertension described in the literature, the malignant phase develops after hypertension has been present in a benign form for some time[6,11,13,14,16,18]. Malignant hypertension may appear quite suddenly in patients who for many years have had renal disease without apparent high blood pressure[11,12]. Onset of the disorder usually is described as associated with severe headaches, visual disturbances, anorexia, vomiting, weight loss and weakness[11,15,16].

However, not infrequently the early manifestations of malignant hypertension are atypical and misleading[14,15]. Our interest in this matter was aroused after encountering several patients who experienced spontaneous gross urethral bleeding, that is, urethral apoplexy, either as the initial or an early manifestation of this condition. This report outlines the pertinent historical, clinical and laboratory findings in four of these patients.

Case Reports. CASE NO. 1: D. D., a 20-year old unmarried white male clerk, was admitted on Nov. 15, 1951, complaining of severe generalized throbbing headaches, increasing weakness and bilateral flank pain. During hospitalization elsewhere, within the year, he had been told he had Bright's disease. Immediately prior to this admission he experienced sudden onset of bleeding from the urethra while sleeping. The hemorrhage was described as painless with bright, red, blood sufficient to soil the bed clothing. On admission the blood pressure was 220/160, grade IV retinopathy with papilledema was noted and the blood urea nitrogen was 168 mg. per 100 cc. Urinalysis revealed 4 plus albumin, numerous leukocytes, and occasional erythrocytes. Other clinical and laboratory findings were similar to those of chronic glomerulonephritis with malignant hypertension. He was allowed to return home on supportive therapy.

When readmitted one month later, he presented severe anterior chest pain, bilateral flank pain, hematuria, increasing uremia and the findings of congestive heart failure. The blood pressure was 230/170. From this period on, the course was progressively downhill with death occurring at home on March 5, 1952. Necropsy was not obtained.

CASE NO. 2: F. H., a 45-year old, white married attorney, was admitted on Mar. 7, 1951. Hypertension was first noted during a routine physical examination in 1942. The condition was essentially asymptomatic with mild sedation. In November, 1950, painless gross bleeding from the urethra occurred with spontaneous clearing in 24 hours. One month later, following a second hemorrhage, the anterior urethra was found to be the site of the bleeding after urological examination including cystoscopy. Intravenous pyelography demonstrated impaired renal function and the patient was hospitalized for evaluation and definitive treatment. On admission the blood pressure was 208/120. There was grade IV retinopathy with papilledema. Urinalysis revealed 2 plus albumin, occasional leukocytes and numerous erythrocytes per high power field. The nonprotein nitrogen was 65 mg. per 100 cc. There was electrocardiographic and fluoroscopic evidence of left ventricular hypertrophy. Dyspnea responded to digitalization, and veratrum therapy was initiated. The re-

sponse to veratrum was not encouraging and the patient was released on Mar. 13, 1951, to pursue dietotherapy elsewhere. It was reported that although there was initial improvement the azotemia and hypertension progressed. Death occurred suddenly on Mar. 28, 1951.

At necropsy, an area of hemorrhage was present in the pons. There were notable old ischemic changes within the cortex and basal ganglia. Petechial hemorrhages were present in the lungs and myocardium. No hemorrhagic lesions of the genito-urinary tract were noted. Microscopically there was pronounced arteriolonephrosclerosis, fibrinoid necrosis of the small arteries, and hyaline necrosis of the arterioles.

CASE NO. 3. R. B., a 33-year old single white male research chemist, was admitted on Oct. 24, 1949. He had been asymptomatic until January, 1949, when spontaneous painless urethral hemorrhage occurred. Urological examination, including cystoscopy, revealed no source of hemorrhage other than the urethra. During the succeeding months he began to feel run down and had minor episodes of laryngitis and an attack of virus pneumonia. One week prior to admission the urological work up was repeated and again found negative. At that time the systolic blood pressure reportedly was 200 mm. Hg. The day prior to admission the only complaint was severe headaches of 3 to 4 weeks' duration. The blood pressure was 285/200. There was grade IV retinopathy with papilledema. Hospitalization was precipitated by the development of a right hemiplegia.

On admission the blood pressure was 240/160. Urinalysis revealed 3 plus albumin, 3 to 5 leukocytes and numerous erythrocytes per high power field. The nonprotein nitrogen was 51 mg. The respiration was Cheyne-Stokes in type. Further clinical and laboratory studies confirmed the diagnosis of malignant hypertension with right hemiparesis. The blood pressure was 220/160 the day of discharge. The patient succumbed at home on Nov. 18, 1949. Necropsy was not obtained.

CASE NO. 4. I. L., a 29-year old, single white male bookkeeper, was admitted on Mar. 15, 1952. The patient enjoyed good health until albuminuria was discovered at Selective Service examination in 1941. In 1947, when hypertension was first reported, his only complaint was severe headache. During the 6 months prior to admission he had easy fatigability, scotomata, loss of visual acuity and some loss of memory. He had been observing a rice diet during this period with little improvement. At admission the blood pressure was 270/160. There was grade IV retinopathy, diastolic gallop rhythm, and electrocardiographic evidence of left ventricular strain and hypertrophy. The urine contained 2 plus albumin, 2 to 3 leukocytes per high power field, and occasional casts. The blood urea nitrogen was 24 mg. A brief episode of painless gross urethral bleeding occurred on the 11th hospital day. No other source of this hemorrhage was found. In view of the failure to respond to hexamethonium and veratrum, a left dorsal sympathectomy was done on Mar. 31, 1952, and on April 11, 1952 right thoracolumbar sympathectomy and right adrenalectomy were carried out. On May 20, 1952, the blood pressure was 170/110 and there was considerable subjective improvement. The patient was released on June 18, 1952, and is known to be alive and doing well at the time of preparation of this report.

Discussion. It is apparent that urethral bleeding was one of the initial symptoms of malignant hypertension in 3 of these patients and occurred early in the hospital course of the fourth. In 2 instances the site of bleeding seems to have been localized to the anterior urethra. All 4 of these patients had significant azotemia. It is of interest that the hemorrhage was observed only in association with renal insufficiency as manifest by nitrogen retention.

The occurrence of petechial hemorrhages within the viscera and gross hemorrhage from the gastrointestinal tract[2] and kidney[14,16] is common in the accelerated phase of malignant hypertension, and is mentioned prominently in several series[6,11,13]. Hemorrhage from the upper genito-urinary tract or kidney may be unilateral[14] and in one instance this misleading sign led to nephrectomy[17]. However, gross hemorrhage from the lower genito-urinary tract is not generally recognized as being associated with malignant hypertension. A limited review of the literature fails to uncover reference to the occurrence of frank, lower, genito-urinary tract bleeding localized to the anterior urethra[1,4,5,13,14,15,18].

Certain of the published data on experimental hypertension in animals contains information that may be pertinent to our observations in man[8]. Unilateral renal artery occlusion in rats has been shown to produce hypertension in association with acute diffuse arterial lesions involving the heart, lungs, gastrointestinal tract, adrenals, kidneys and central nervous system. However, in no instance were the arterial lesions demonstrated in the lower genito-urinary tract[3].

Goldblatt's[7] report of his investigation of the malignant phase of experimental hypertension permits review of each experimental animal. Among these were 5 hypertensive dogs with azotemia, 4 of which had petechial or ecchymotic urinary bladder hemorrhages, while the fifth animal appeared to have both bladder and urethral hemorrhages[7]. Another investigator[9] produced necrotizing arteritis in the absence of hypertension in animals, with experimental renal insufficiency, which were fed a high fat diet. Hemorrhagic phenomena were observed in the urinary bladder in 90% of these animals. This experimental evidence, in addition to our patient observations, suggests that renal insufficiency may be a factor in the urethral bleeding seen in these hypertensive subjects.

The localization of histo-pathologic changes in the arterioles is generally accepted as typical of malignant hypertension[10]. However, there is less agreement on the criteria for the characteristic lesion[13]. That the hemorrhages in our patients were due to necrotizing arteriolitis seems most probable. Their localization in the urethra appears important both clinically, since appreciation of their occurrence might allow earlier diagnosis, and theoretically, since their unusual location may aid in further appraising the fundamental vascular lesion of the disease.

Summary. 1. Four patients with hypertension in the malignant phase have been presented. In each instance spontaneous urethral bleeding was either the initial symptom or appeared early in the disease.

2. The infrequency of the reported occurrence of urethral hemorrhage associated with malignant hypertension has been emphasized.

3. The occurrence of bladder and urethral hemorrhages in experimental hypertension and experimental renal insufficiency is noted and its possible relation to human findings is discussed.

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THE ACTION OF HYDERGINE ON THE CIRCULATION AND METABOLISM OF THE BRAIN IN TOXEMIA OF PREGNANCY†

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It has been demonstrated that the cerebral vascular resistance is increased in patients with toxemia of pregnancy[10]. In our quest for an agent which will safely and successfully relax this vasospasm we are endeavoring to study a variety of vasodilating substances with differing modes of action[11,12].

Ergot, for centuries known and used as an oxytocic agent in obstetrics, was shown by Dale[5] in 1906 also to possess sympathetic inhibiting ability. The latter action of this drug, however, has been overshadowed almost completely by its marked stimulating effect upon smooth muscle. Recently Stoll and Hoffman[15] isolated 3 new ergot alkaloids which, when dihydrogenated, became strong sympathetic inhibitors and vasodilators without the usual oxytocic or smooth muscle effect. These three compounds, dihydroergocornine, dihydroergocristine and dihydroergokryptine have been combined and marketed under the name Hydergine.‡ It is the purpose of this paper to report the effects of Hydergine on the circulation and metabolism of the brain in toxemia of pregnancy.

Methods and Materials. The method of Kety and Schmidt[9] was used. This involves the simultaneous withdrawal of venous blood from the internal jugular bulb and arterial blood from the femoral artery over a period of 10 minutes while the patient is breathing a mixture of 15% nitrous oxide, 21% oxygen and 64% nitrogen. Mean arterial blood pressure is measured directly from the femoral artery with a damped mercury manometer. Blood gas analyses of nitrous oxide, oxygen and carbon dioxide are made with the Van Slyke-Neill apparatus.

As previously described[10], cerebral blood flow (CBF) is measured in cubic centimeters per 100 gm. of brain per minute. Cerebral oxygen metabolism (CMRo2)* may then be calculated in cc. of oxygen utilized per 100 gm. of brain per minute, and cerebral vascular resistance (CVR)** in millimeters of mercury pressure per cc. of blood flow per 100 grams of brain per minute. The respiratory quotient (RQ)*** is calculated by computing the relationship between the oxygen uptake by the brain and the amount of carbon dioxide given off.

Thirty investigations were carried out on 15 women in the latter weeks of pregnancy or

$$*CMRo2 = CBF \times \frac{(A - V)o2}{100}$$

$$**CVR = \frac{MABP}{CBF}$$

$$***RQ = \frac{(V - A)Co2}{(A - V)o2}$$

†This study was supported in part by a research grant from the Sandoz Pharmaceutical Company.

‡Hydergine is a product of the Sandoz Pharmaceutical Company and was furnished for this study through the courtesy of their Division of Research.

the early puerperium; 7 were normal pregnant women and 8 were afflicted with toxemia of pregnancy. Of the latter group 4 had pure preeclampsia and 4 had acute toxemia superimposed upon pre-existing hypertension. No therapy was given for at least 12 hours before the control flow (c). Immediately after the first flow 2 cc. (0.6 mg.) of Hydergine (C.C.K.179) were administered intramuscularly. The investigation was then repeated when the hypotensive effect was most marked. The interim between control and experimental flows (e) averaged 47 minutes and varied from 30 to 90 minutes after administration of the drug. Restlessness and nasal congestion were common complaints, whereas vomiting occurred in only 2 patients. There were no serious reactions.

Results. Table 1 summarizes the tests done upon each of the patients in both the toxemic and normal pregnant groups. Mean arterial blood pressure was lowered 15% in normal pregnant women and 18% in patients with toxemia, while cerebral vascular resistance was decreased 12.5% in the normal group and 15% in the toxemic group of patients. These changes were statistically significant. The blood gases, cerebral blood flow, oxygen uptake by the brain and respiratory quotient of the brain were unaffected by the administration of Hydergine.

Discussion. These studies show that the increased vascular resistance within the brain in toxemia of pregnancy is partially relieved by the intramuscular dosage of a mixture of dihydrogenated ergot compounds known as Hydergine. The systemic blood pressure is also significantly lowered while cerebral blood flow and oxygen metabolism are maintained at normal levels.

There are 2 main mechanisms which bring about the hypotensive action of these compounds. Rothlin[13] showed that there is a direct depression of the vasomotor center and stimulation of the "vasodepressor" center in the medulla. The importance of this mechanism has been emphasized by Bluntschli[2] who demonstrated that spinal section in animals almost completely abolishes the hypotensive effect of ergot compounds.

On the other hand adrenergic blocking properties are also present. The previously mentioned work of Dale[5] and that of Sollmann and Brown[14] in 1905 were the first to show this effect of crude ergot preparations, while Rothlin[13] discovered that the dihydrogenated ergot compounds possess this type of action also. How much the latter mechanism comes into play in pregnancy toxemia is problematic. It has been shown by Assali and Prystowsky[1] that there is no circulating sympathomimetic substance present such as epinephrine or norepinephrine to account for the vasoconstriction and hypertension of toxemia of pregnancy. We must therefore assume that the generalized vasodilation brought about by Hydergine is mediated through central effect upon the vasomotor centers or by blockade of sympathetic vasoconstrictor impulses.

The exact mechanism which produces cerebral vasodilatation is still in doubt. The possibility of adrenergic blockade of vasoconstrictor impulses to the vessels of the brain must be considered. The fact that bilateral stellate ganglion block[8] fails to produce such an effect, however, weakens the evidence that there is vasoconstrictor tone of these vessels mediated through the sympathetic nervous system. It seems more probable that vasodilator pathways are being utilized through the facial and superficial petrosal nerves as described by Chorobski and Penfield[3] in 1932.

Hafkenschiel and his associates[7], also using the nitrous oxide method for cerebral blood flow, found that patients with essential hypertension when given dihydroergocornine had considerable reductions of mean arterial blood pressure and cerebral vascular

TABLE 1.—EFFECTS OF HYDERGINE ON BLOOD GASES AND CEREBRAL FUNCTION*

				Cerebral								Oxygen content vol. %				Carbon dioxide vol. %					
		MABP mm. Hg		cc./100 gm. brain/min. CBF		CMRo2		CVR / MABP / CBF		RO		Femoral artery		Internal jugular		Femoral artery		Internal jugular		A-Vo2 vol. %	
Patient	Diagnosis	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
S. O.	Normal	103	83	66	57	4.6	4.0	1.5	1.4	1.1	1.0	15.4	15.5	8.4	8.4	35.8	36.9	43.3	44.1	7.0	7.1
V. K.	Normal	104	92	64	49	4.4	3.0	1.6	1.9	1.1	.98	14.3	12.4	7.4	6.3	32.0	36.7	39.0	43.4	6.9	6.1
F. N.	Normal	100	89	52	55	3.1	3.4	1.9	1.6	.93	.92	15.3	15.9	9.4	9.8	29.1	29.4	34.6	35.0	5.9	6.1
L. E.	Normal	97	93	48	53	3.0	3.4	2.0	1.8	1.04	1.02	13.5	13.7	7.2	7.3	42.0	42.6	48.6	49.1	6.3	6.4
G. H.	Normal	95	76	52	57	3.3	3.7	1.8	1.3	1.0	1.0	15.1	15.3	8.7	8.9	43.2	43.3	49.6	49.8	6.4	6.4
D. W.	Normal	52	36	57	56	3.7	3.6	0.9	0.6	1.0	1.0	13.7	13.9	7.2	7.4	40.9	41.5	47.4	48.0	6.5	6.5
J. H.	Normal	91	76	54	59	3.4	3.7	1.7	1.3	1.0	0.98	16.0	15.8	9.7	9.5	49.5	49.0	55.8	55.2	6.3	6.3
S. H.	Hypertensive	169	102	55	42	3.6	3.6	3.0	2.4	.98	1.1	14.1	14.5	7.5	7.8	42.7	42.2	49.2	49.4	6.6	6.7
L. D.	Hypertensive	111	103	46	41	2.9	2.8	2.4	2.5	1.0	.91	16.0	16.7	9.8	9.8	39.6	38.8	43.4	45.1	6.2	6.9
V. W.	Preeclampsia	138	107	53	59	3.2	4.1	2.6	1.8	1.1	1.0	12.6	13.6	6.5	6.7	41.3	41.4	47.8	48.4	6.1	6.9
L. B.	Hypertensive	166	150	54	63	3.5	3.9	3.1	2.4	.95	.95	16.7	16.5	10.2	10.2	43.9	44.4	50.1	50.4	6.5	6.3
A. P.	Hypertensive	131	112	49	53	3.1	3.1	2.7	2.1	1.03	.97	13.6	13.1	7.2	7.3	42.6	43.4	49.2	49.0	6.4	5.8
O. T.	Preeclampsia	125	92	46	48	3.5	3.6	2.7	1.9	.94	.87	15.2	14.7	7.6	7.2	36.0	36.4	43.2	42.9	7.6	7.5
P. G.	Preeclampsia	112	94	51	56	3.2	3.2	2.0	1.7	1.1	.94	16.7	16.4	11.1	10.7	45.9	46.3	52.1	51.7	5.6	5.7
L. B.	Preeclampsia	100	107	51	44	2.8	2.4	1.9	2.4	1.0	.99	11.9	12.7	6.4	7.2	44.9	44.6	50.4	50.0	5.5	5.5
Mean values of toxemic patients		132	108‡	51	51	3.2	3.3	2.6	2.2†	1.01	0.97	14.6	14.8	8.3	8.4	42.1	42.2	48.2	48.4	6.3	6.4
Mean values of normal pregnant women		92	78‡	56	55	3.6	3.5	1.6	1.4†	1.02	0.99	14.8	14.6	8.3	8.2	38.9	39.9	45.5	46.4	6.5	6.4

* MABP = Mean arterial blood pressure
CBF = Cerebral blood flow
CMRo2 = Cerebral oxygen metabolic rate
CVR = Cerebral vascular resistance
RQ = Respiratory quotient

C = Control flow
D = Flow under influence of Hydergine

†—Statistically significant change $p<0.05$
‡—Statistically significant change $p<0.01$

resistance while blood flow and oxygen metabolism remained normal. The similarity of their findings in essential hypertension and ours in toxemia of pregnancy is striking. We feel as they do that there is a definite action upon the brain in addition to the block of sympathetic vasoconstrictor influences elsewhere in the body, and that the resultant decrease in vascular resistance within the brain allows for cerebral vascular and metabolic homeostasis.

Hydergine, however, apparently hinders homeostasis in certain other parts of the body. There is a loss of vasomotor compensation for upright tilting and the immersion of portions of the body in iced water[6]. Such hampering of adaptive influences deprives the patient of the normal safeguards ordinarily vouchsafed by vasomotor lability and greatly increases the danger of circulatory collapse. Renal physiology is also interfered with as demonstrated by the decrease of effective renal plasma flow and glomerular filtration rate[4] as well as oliguria on the basis of increased tubular reabsorption of water.

Nevertheless, the fact remains that homeostasis is maintained within the brain in spite of circulatory aberrations elsewhere when Hydergine is given. We may conclude, therefore, that the dihydrogenated ergot compounds do not interfere with the ability of the human mechanism to compensate its internal environment in such a way that blood may be diverted from less important areas of the body to the more essential brain.

Summary. 1. Quantitative studies of cerebral blood flow, cerebral oxygen metabolism, cerebral vascular resistance, mean arterial blood pressure, respiratory quotient of the brain and the blood gases were made in both normal and toxemic pregnant women before and after the administration of Hydergine.

2. Cerebral vascular resistance and mean arterial blood pressure were significantly depressed in both groups of patients.

3. Cerebral blood flow, cerebral oxygen metabolism, respiratory quotient of the brain and the oxygen and carbon dioxide content of femoral arterial and internal jugular venous blood were unaffected by the administration of Hydergine.

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ELECTROCARDIOGRAPHIC PATTERN SIMULATING ACUTE MYOCARDIAL INJURY

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Abnormal displacement of the S-T segment may be associated with a variety of clinical states. In myocardial injury the typical configuration consists of elevation and upward bowing of the S-T segment with symmetrical inversion of the T waves in leads facing the affected area. We have recently observed a similar electrocardiographic pattern in patients without clinical evidence of any acute myocardial process. The purpose of this paper is to point out the distinguishing characteristics of this pattern and to elucidate the mechanism of its production.

Our attention was first drawn to this pattern by the electrocardiograms reproduced in Figure 1. The patient, a 39-year-old white male, entered the Beth Israel Hospital for study on January 19, 1950, because of an episode, 2 weeks previously, of interscapular pain following exertion, and vague substernal discomfort 2 days prior to admission. Physical examination was entirely within normal limits with blood pressure of 120/80 and a normal sized heart with sounds of good quality and no murmurs. Chest roentgenogram and laboratory examination of urine and blood revealed no abnormalities. His hospital course was afebrile and symptom-free except for anxiety; there was no further chest pain and white blood cell counts and erythrocyte sedimentation rates remained normal. Initial electrocardiograms showed right bundle branch block (RBBB) with elevation of S-T segments and inversion of T waves in the right precordial leads, and were interpreted as consistent with anteroseptal injury. However, subsequent tracings showed persistence of the S-T-T pattern with only minor variations, rather than the serial changes typical of evolution of an acute process. The patient was discharged on February 6, 1950, and remained well for 8 months.

In November, 1950, during a period of emotional turmoil, he was again hospitalized because of mild substernal discomfort lasting one day. Clinical and laboratory examination failed to reveal any abnormality, and his hospital course was uneventful except for a few brief twinges of chest pain related to emotional upsets. The electrocardiograms were essentially unchanged and again failed to show progressive changes. The patient has remained well to date (April, 1953), and presents no objective evidence of heart disease although the unusual electrocardiographic pattern persists.

Figure 2 shows the electrocardiograms of a healthy 43-year-old white male (H.D.E.S. Case Number 4549)

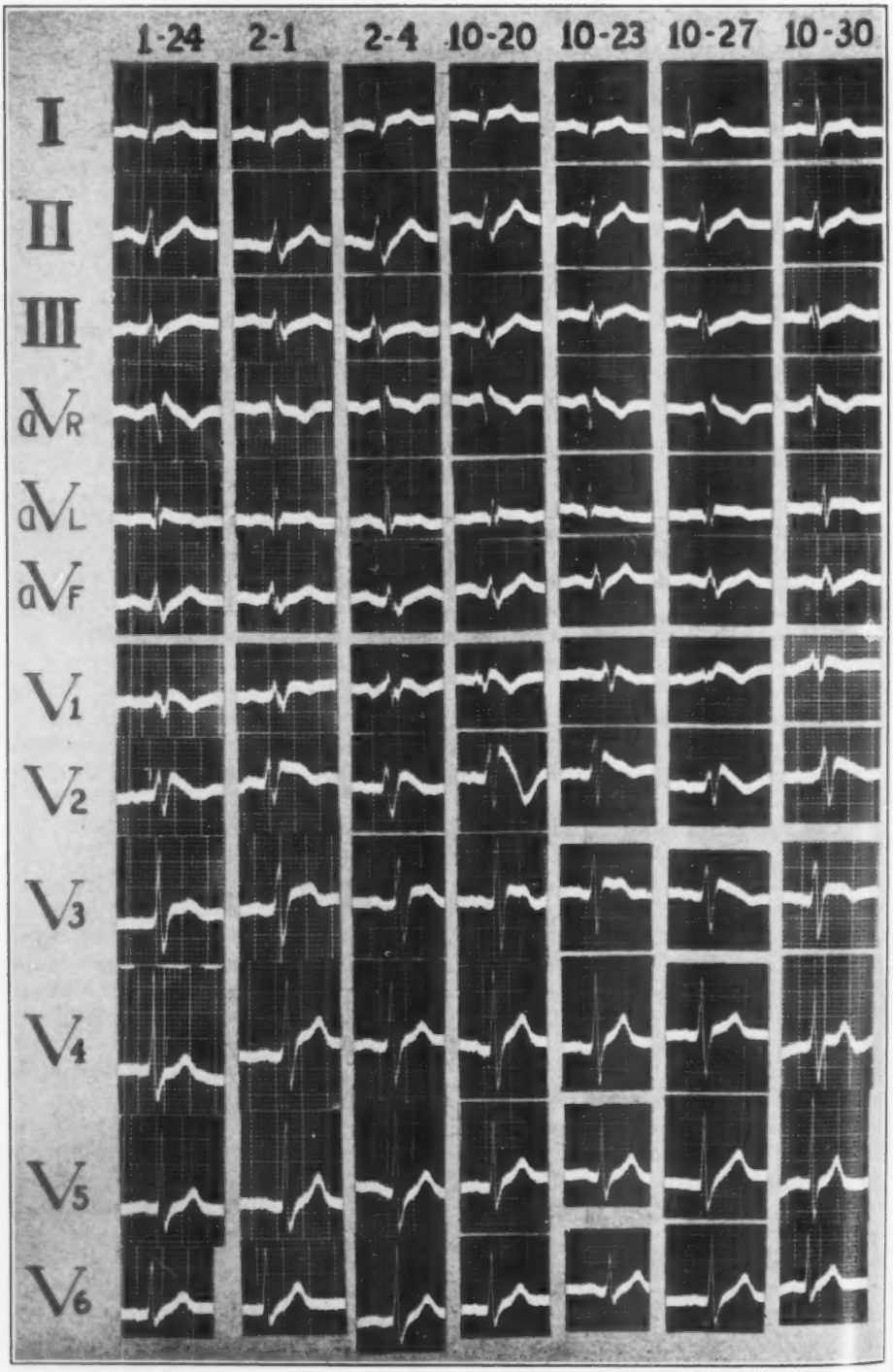

Fig. 1.—Electrocardiograms of a 39-year-old white male with mild atypical chest pain but no clinical evidence of heart disease. Note the wide QRS interval (0.12-0.13 sec.) with features of RBBB, and S-T segment elevation and T wave inversion in the right precordial leads, simulating the pattern of anteroseptal injury. The serial tracings show minor variations in the S-T-T configuration, but not the typical evolution seen with myocardial injury.

who was examined during a cardiovascular disease survey. Examinations in January, 1951, and January, 1953, disclosed no symptoms or signs of cardiac disease. The electrocardiograms are similar to those of the previous patient, showing RBBB with elevated S-T segments and inverted T waves in the right precordial leads. The pattern remained essentially unchanged over a 2-year follow-up period.

tials arising from depolarization of the ventricles. The normally isoelectric S-T segment represents the interval when depolarization has been completed and the potentials associated with repolarization have not yet attained sufficient magnitude to be registered. The latter are expressed in the T wave.

If by the time the depolarization process has reached the last regions of the ventricles, repolarization of regions

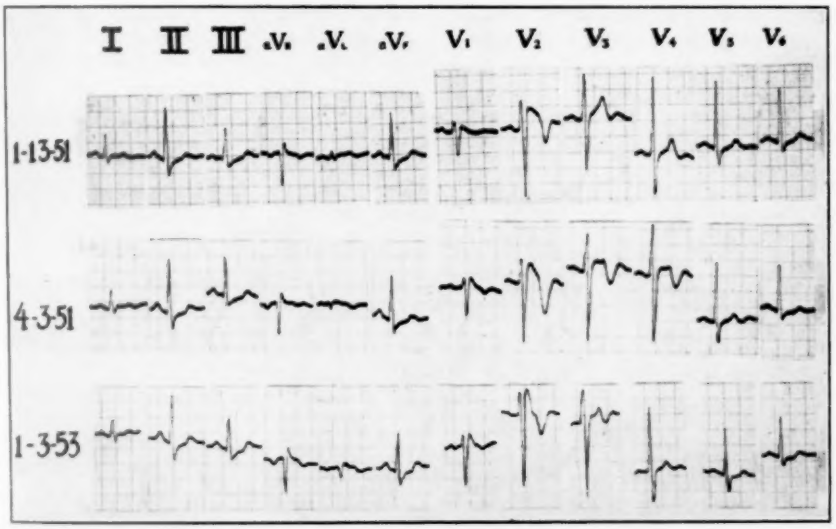

Fig. 2.—Electrocardiograms of a healthy 43-year-old white male with no clinical evidence of heart disease. Note the pattern of RBBB with S-T segment elevation and T wave inversion in the right precordial leads. The S-T segment is more clearly defined in leads V_1 and V_2 of the last tracing than in the previous two. (The apparent change in T_{V_4} of the second tracing is due to a difference in electrode placement, as evidenced by the associated change in QRS configuration.)

Figure 3 shows the electrocardiograms of a healthy 37-year-old white male (H.D.E.S. Case Number 2989) with no clinical or laboratory signs, other than the electrocardiogram, of cardiovascular disease. The tracing shows incomplete RBBB with an S-T-T configuration similar to that of the previous cases.

Discussion. The QRS complex of the electrocardiogram reflects potentials arising from depolarization of the ventricles. The normally isoelectric S-T segment represents the interval when depolarization has been completed and the potentials associated with repolarization have not yet attained sufficient magnitude to be registered. The latter are expressed in the T wave.

If by the time the depolarization process has reached the last regions of the ventricles, repolarization of regions activated earlier is sufficiently advanced to produce significant potentials, deviation of the S-T segment will occur. This is presumed to be one of the mechanisms of the slight S-T segment deviations sometimes seen normally, and those seen in a number of clinical conditions including tachycardia and intraventricular conduction disturbances. In the latter condition the S-T segment is deviated in the

direction opposite to that of the main QRS deflection. It is usually possible to distinguish the junction (J) of the QRS complex and the S-T segment because of an abrupt change in direction of the tracing.

Secondary T wave alterations in intraventricular conduction disturbances are due to the changed sequence of repolarization consequent to the altered sequence of depolarization. The larger the increase in the net area of the QRS complex, the greater is the tendency for the T wave to become oppositely directed to the QRS. Thus, the S-T segment and T wave are deviated in the same direction.

Sublethal injury may produce partial or complete depolarization of resting myocardium, may render it electrically unresponsive or incapable of depolarization, or may delay or prolong repolarization of activated myocardium. Alteration of the resting state of polarization or of the ability to respond results in injury currents in the resting and activated states, respectively, producing deviation of the S-T segment in each instance. Interference with recovery causes an injury current of repolarization, giving rise to primary T wave changes[1].

As noted previously, myocardial injury classically produces elevation and upward bowing of the S-T segment and pointed, symmetrical inversion of the T wave; that is, the S-T segment and T wave are deviated in opposite directions. Further, this pattern is unstable, the S-T segments returning to the isoelectric level in several hours or days as the myocardial injury subsides. The T waves may remain abnormal or may return partially or completely to normal over a period of days or weeks, depending upon the degree and duration of injury and the extent of recovery.

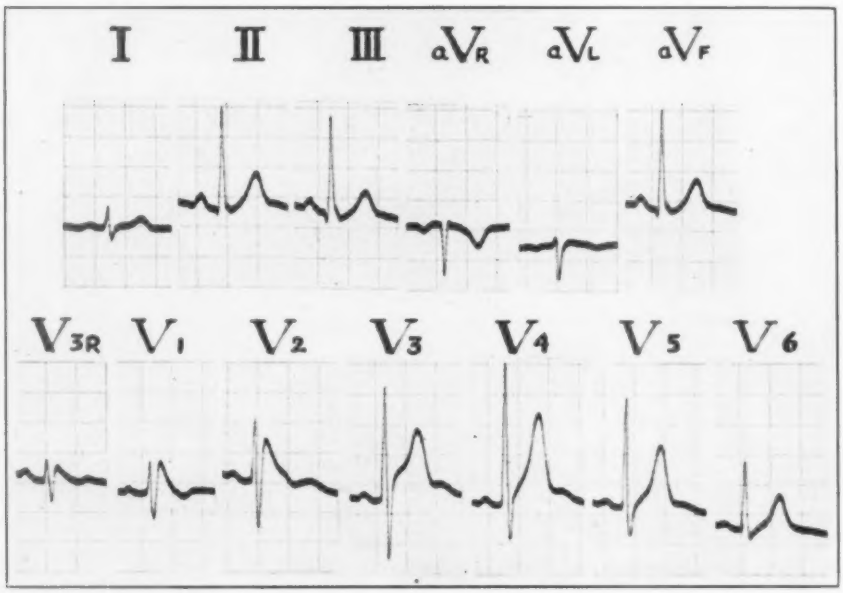

Fig. 3.—Electrocardiogram of a healthy 37-year-old white male with no clinical evidence of heart disease.

The tracings described above display the following characteristics: (1) the QRS interval is prolonged or at the upper limit of normal, (2) there are small R, moderate or deep S and prominent wide R′ deflections in the right precordial leads, and broad S waves in lead I and the left precordial leads: the typical configuration of RBBB, (3) the R′ deflections merge imperceptibly with the S-T-T complex in a smooth, sometimes coved, descending line so that it is difficult to locate the junction of QRS and S-T, or to delineate the S-T segment; the over-all appearance simulates that of an elevated S-T segment, (4) the right precordial T waves are inverted or diphasic, (5) polarization and repolarization, manifested by fusion of the terminal portion of the QRS complex with the initial portion of the S-T-T complex. This is apparently due to prolongation of the depolarization process by right bundle branch block or possibly focal block with delayed activation of a portion of the right ventricle: unusually early onset of repolarization may also play a role. Since the terminal portion of the QRS complex in the right precordial leads consists of a broad R′ deflection, the origin of the S-T segment is elevated and obscured. The associated T wave is inverted, as is usual in right precordial leads showing the RBBB configuration.

TABLE 1.—RIGHT PRECORDIAL S-T-T CONFIGURATION IN VARIOUS CONDITIONS

	Acute anteroseptal injury	*Uncomplicated RBBB*	*Pattern described in this paper*
S-T Segment	Elevated (opposite to T wave)	Depressed (same direction as T wave)	Elevated (opposite to T wave)
T Wave	Symmetrically inverted	Usually inverted (opposite main QRS deflection)	Inverted (opposite main QRS deflection)
Constancy of Pattern	Serial changes toward normal	Constant	Constant

the pattern remains constant or shows only minor variations over long periods of observation.

Thus, this pattern differs from the usual RBBB pattern in that the S-T segments and T waves are deviated in opposite directions. It resembles the pattern resulting from acute injury in this regard, but fails to undergo the usual process of evolution; the minor variations observed in serial tracings may be attributable to differences in precordial electrode placement. Table 1 summarizes the diagnostic features in each condition.

It is suggested that this pattern results from overlapping of ventricular activation and recovery with simultaneous recording of potentials due to de-

Widening of the QRS complex and fusion of its terminal portion with the T wave has been described in association with potassium intoxication. However, none of the conditions commonly associated with hyperpotassemia was present in any of the patients described above, and a blood potassium determination in Case 2 was within normal limits.

Summary. An electrocardiographic pattern resembling that occurring in acute anteroseptal injury with RBBB has been observed in healthy individuals. It is suggested that this configuration results from the overlapping of terminal depolarization and initial repolarization potentials.

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THE EFFECT OF PRISCOLINE UPON NORMAL AND DIABETIC GLYCEMIA*

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It is a well known fact that intercurrent diseases markedly affect the course of diabetes mellitus. With very few exceptions the diabetic state is aggravated by the development of the complication and improved with its subsidence. This phenomenon, which is considered a reaction to stress and its relief, is generally not related to the specific character of the complicating disease nor to the mode of its treatment. In some instances, however, the question arises whether the therapeutic procedure used in combatting the complication may not have a direct and specific ameliorating effect upon the underlying diabetes. The antiadrenergic and sympathetic blocking agents used in peripheral vascular disease pose such a problem.

The medical management of the peripheral vascular disturbances associated with diabetes has been advanced significantly by the introduction of these vasodilator drugs. It has been suggested that the same mechanism by which they achieve increased peripheral blood flow may have an effect upon the autonomic nervous control of carbohydrate metabolism and inhibit insulin antagonists.

A number of reports have been presented to show the insulin sparing effect of Priscoline. These observations, however, were made under complex clinical situations and do not permit critical evaluation. It is questionable whether the diabetic improvement was a direct result of the medication or a nonspecific reaction accompanying the treatment and amelioration of the complicating peripheral vascular disease.

Rogers[2] and Cattaneo[1] noted the development of insulin reactions and marked decrease in the insulin requirement during Priscoline treatment of arteriosclerotic leg ulcers in diabetic patients. Unger[5] described improvement of the diabetic glucose tolerance. Sasson[3] reported a gradual decrease in the hyperglycemia and glycosuria in 20% of his diabetic patients under Priscoline, but he stated that a number of these patients suffered from complications as ulcers of the legs or toes, carbuncles, cystitis or neuritis. In our own clinical material, which consists mainly of elderly diabetic patients with various types of peripheral vascular complications, we make wide use of the vasodilator drugs, orally or intramuscularly, and have often observed the concomitant improvement of the diabetes. Here too, however, the vasodilator is usually only a part of the therapeutic program. The following case report is given, not only to illustrate our own experiences, but more

*The Priscoline was kindly supplied by Ciba Pharmaceutical Products, Summit, New Jersey.

so to demonstrate how difficult it is to arrive at definitive conclusions under complicated clinical conditions.

Case Report. *Pat. F.M.*, was a 64-year-old white male with diabetes of several years duration. (Fig. 1.) He had been fairly well controlled with 20 to 25 units Protamine Zinc Insulin (PZI) daily. For the past 2 years he had complained of pain and paresthesias in both legs. A few days prior to admission the patient noted a vesicle on the big toe of the right foot. On the day of admission the vesicle had opened, the toe and the dorsum of the foot were red, slightly swollen and warm; the patient had fever; the white blood cell count and the sedimentation rate were elevated; the urine showed 4+ sugar and the fasting blood sugar on the following morning was 325 mg. per 100 cc. The blood pressure was 160/90, the peripheral pulsations were diminished in both feet, but good in the popliteal arteries. The fundi appeared normal; the electrocardiogram did not show any abnormalities. The patient was kept at bed rest, the leg was immobilized and the insulin dose increased to 40 units of PZI. Penicillin 600,000 u/day and Priscoline 50 mg. every 4 hours (300 mg./day) were given intramuscularly. Within a few days the inflammatory reaction was under control. The antibiotic was discontinued on the 10th day. During continued Priscoline medication the ulcerative lesion of the toe began to heal and the blood sugar and glycosuria decreased gradually. Insulin could be reduced to a dose of 15 units PZI/day, that is, somewhat lower than that which the patient had taken before the complication had begun.

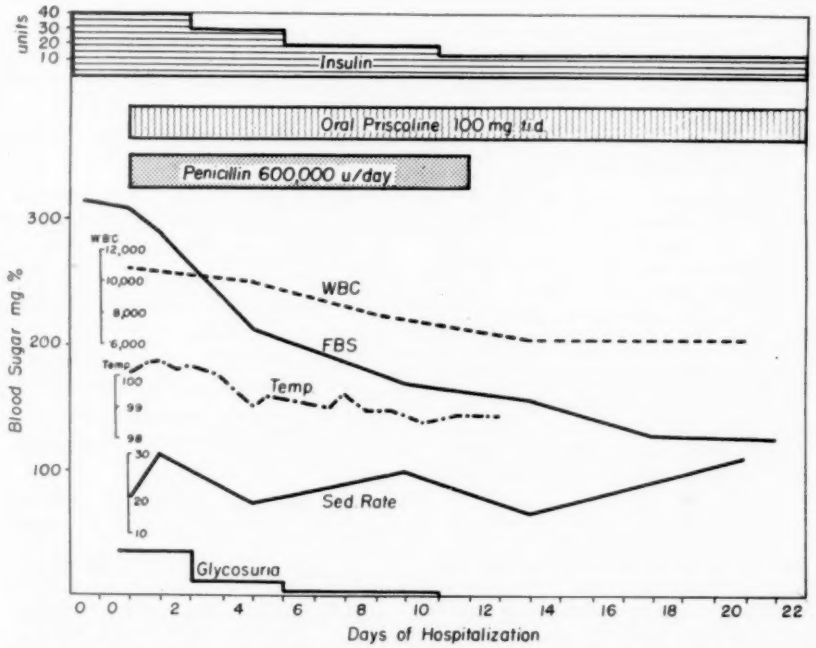

Fig. 1.—Patient F.M., 64-year-old female. Diabetes mellitus complicated by inflammation and ulceration on right big toe. Course of the disease in the hospital under bed rest, antibiotic and Priscoline medication.

It is evident that numerous factors contributed to the improvement of this patient's diabetes. These were hospitalization and bed rest, better dietary supervision, control of the infection by antibiotics, and improvement of peripheral circulation while receiving Priscoline. Under such conditions it is

difficult to evaluate the specific role of any of these factors.

Therefore, we undertook a study of the effect of various doses of Priscoline on the blood sugar level of normal and diabetic animals as well as of non-diabetic patients and those with uncomplicated diabetes. It is obvious that a direct action upon the blood sugar and an insulin sparing effect of the drug should become manifest in the uncomplicated diabetes and the normal organism as well as in diabetes complicated by peripheral vascular disease.

Method and Procedure. Animal experiments were carried out on normal and alloxan-diabetic rabbits of about 2000 gm. body weight. The animals were fasted overnight and then given intramuscular injections of 5 and 10 mg. of Priscoline respectively. Their blood sugar levels were determined at short intervals for a period of 5 hours. Control experiments were done after intramuscular injection of a similar amount of normal saline solution. The same animals were subjected to intravenous glucose tolerance tests using 5 cc. of a 20% glucose solution. Two glucose tolerance tests were performed with each animal, one after intramuscular injection of 10 mg. Priscoline, and another after normal saline administration.

Observations in man were made on 3 groups of patients: a) A selected group of patients with well controlled diabetes without evidence of peripheral vascular disturbance or any other complicating disease. The course of their diabetes was observed for a period of 10 weeks during which they received gradually increasing doses of Priscoline at weekly intervals.

b) A group of children in the recovery phase from acute poliomyelitis who were under treatment with Priscoline.

c) A group of patients with multiple sclerosis in whom the effect of the drug on their neurological disorder was under evaluation.

All 3 groups were hospitalized throughout the observation periods and kept under standard diet and activities.

Results. A. ANIMAL EXPERIMENTS. Neither the normal nor the alloxan-diabetic rabbits showed any significant decrease of the fasting blood sugar level under the influence of 5 or 10 mg. Priscoline intramuscularly. The observed fluctuations of the glycemia during the 5-hour period were similar to those after saline administration.

Different results were obtained with the intravenous glucose tolerance test. Here the blood sugar values after Priscoline showed in all instances a lower curve and a more rapid return to the fasting level than after saline. While in the saline pretreated normal animals the fasting level was reached after 120 minutes, it was attained after Priscoline treatment at 90 minutes; a similar acceleration of the return was seen in the alloxan-diabetic rabbits after Priscoline administration. It is noteworthy, however, that hypoglycemic levels or levels lower than fasting were seen neither in the normal nor in the diabetic animals. It should be mentioned also that these results were obtained with doses of Priscoline relatively far in excess of those used in man.

B. NON-COMPLICATED DIABETES. Ten patients with well controlled and stable diabetes were selected from the hospital wards. Five patients were males, and 5 females; all of them had diabetes for 5 or more years. At the time of selection they were free from any intercurrent disease and did not have signs or symptoms of peripheral vascular insufficiency. Two patients were on dietary management, 8 required insulin and diet. The insulin requirements varied in the various patients between 10 units PZI/day and combinations of short- and long-acting insulins to a total of 45 units/day. During a stabilizing period of one week the adequate control of each patient's diabetes was ascertained. After the first week oral Priscoline medication was started in gradually increasing dosage beginning with 25 mg. twice daily. At weekly or biweekly intervals the dosage was increased to a maximum of 300 mg. daily, which was given either as 50 mg. every 4 hours.

or 100 mg. t.i.d. During each week of the 10 weeks' observation period, the fasting blood sugar was determined twice weekly and urinalysis was carried out daily.

In all patients the fasting blood sugar level showed some fluctuations. These fluctuations, however, did not reveal any significant trend, rather they were typical of the spontaneous variations of the blood sugar levels of 5 of the patients; the levels of the remaining 5 patients were practically identical and are omitted from the graph for technical reasons only.

Further increase of the Priscoline dosage did not seem to be warranted since the clinical observations which suggested a beneficial effect of Priscoline on the diabetic status had been made in patients whose peripheral

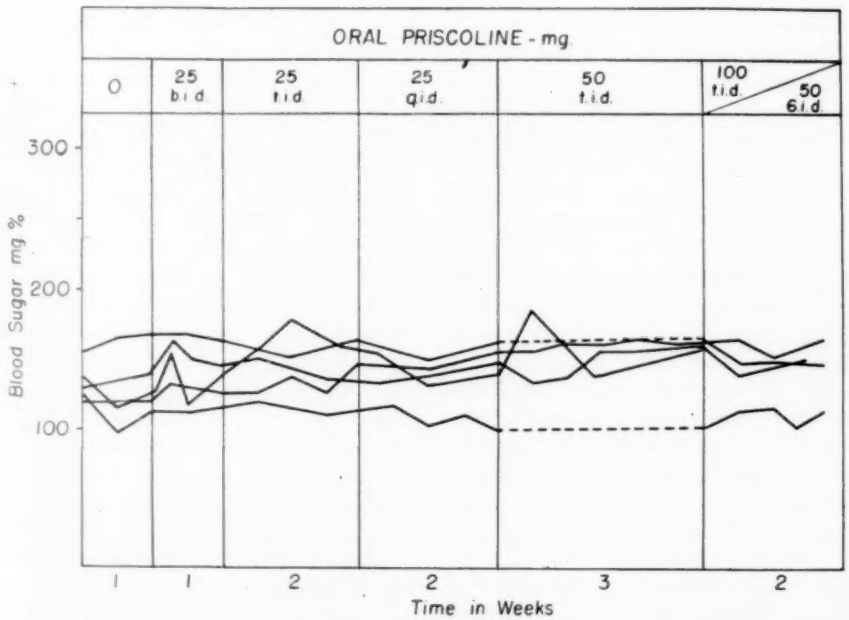

Fig. 2.—The course of the fasting blood sugar level of 5 patients with uncomplicated diabetes under medication with various doses of Priscoline.

even the well controlled diabetic. In no instance did we encounter a hypoglycemic reaction and in none of the insulin treated patients was there any need to reduce the insulin dose. Since all patients had been well controlled at the beginning of the experiment, the glycosuria, if present at all, was minimal.

Figure 2 traces the blood sugar levels throughout the observation period for

vascular complication was treated with doses in this range.

C. NON-DIABETIC PATIENTS. Both the patients with poliomyelitis and those with multiple sclerosis showed fasting blood sugar levels well within the norm. The poliomyelitis patients were under daily medication of 50 mg. of Priscoline every 4 hours intramuscularly; while the patients with multiple sclerosis received varying smaller doses

orally, 25 mg., t.i.d., to 50 mg., t.i.d. The observation period was 4 weeks and blood sugar levels were determined at irregular intervals. In 2 instances the blood sugar was followed for 5 hours after intramuscular administration of 50 mg. Here, too, no abnormally low values were obtained.

The spasmolytic effect of Priscoline as an adjunct in the treatment of poliomyelitis has been described by Smith and his associates[4] and has been seen by us. The results of our studies on its effects in multiple sclerosis will be reported separately.

DRUG TOLERANCE. Only a few words about the drug tolerance. The diabetic patients tolerated the drug rather well up to the maximum dose, but 6 patients began to complain about minor disturbances when they reached a dosage of 6×50 mg. or 300 mg./day. The most common complaint was dizziness; some had flushing of the face, shakiness and headaches. One patient became confused. It was felt that this was due to the drug since the symptoms disappeared with cessation and recurred with reinstitution of the medication. There were only minor fluctuations of the blood pressure. In no instance was it necessary to terminate the experiment prematurely.

This fairly satisfactory tolerance of the drug by the uncomplicated diabetic patient is in contrast to the unexpected and so far unexplained high intolerance of patients with multiple sclerosis. These patients almost invariably complained about flushing of the face and skin, headaches and about muscular stiffness and rigidity. When doses as low as 25 mg. were used, these reactions still persisted for as long as 2 to 3 hours. In some of these patients the drug had to be discontinued permanently and the rest felt most uncomfortable when 3×50 mg. were given.

The reactions of the post-poliomyelitis patients were still different. All of these patients tolerated the medication of 6×50 mg./day well without the slightest complaint. This is all the more remarkable since most of them were young children and the dosage, therefore, relatively far higher than in the adult patients with diabetes or multiple sclerosis.

This difference in drug tolerance in various disease states needs further investigation.

Discussion. Our animal experiments demonstrate that appropriate doses of Priscoline accelerate the disposal of glucose in the intravenous glucose tolerance test. This was seen in the normal rabbit as well as in the alloxan-diabetic rabbit. This finding confirms Unger's[5] observation in diabetic patients. On the other hand, Priscoline failed to show any effect upon the fasting blood sugar level of the experimental animal, patients without diabetes, or with uncomplicated diabetes. It also failed to induce a secondary hypoglycemia in the glucose tolerance test, which should be expected if the accelerated glucose disposal were due to unopposed action of insulin. The findings rather suggest an alternate explanation; namely, that the increased peripheral blood flow induced by Priscoline permits indirectly a more rapid removal of the injected glucose from the blood stream. When the blood sugar is normal or slightly elevated, this phenomenon apparently does not become manifest because of the homeostatic mechanism.

The beneficial effect upon the diabetes which is so frequently noted when a peripheral vascular complication responds to treatment with vasodilator drugs must, therefore, be considered as an indirect result. By alleviating the complicating condition, the drug ameliorates the metabolic and endocrine stress, and thus secondarily improves the diabetic state. This con-

clusion does not minimize the important functions which the vasodilators have in the medical management of peripheral vascular disease complicating diabetes. Important as it is to know the specific actions and limitations of our therapeutic agents, in the practical situation it makes little difference whether a therapeutic result is obtained by direct action or indirectly.

Summary and Conclusions. 1. Priscoline does not affect the fasting blood sugar level of normal or diabetic rabbits, or of non-diabetic patients and patients with uncomplicated diabetes.

2. Priscoline tends to accelerate the disposal of intravenously injected glucose in normal and diabetic rabbits but does not induce hypoglycemia.

3. The improvement of the diabetic state during the medical management of a peripheral vascular complication with vasodilator drugs is considered to be an indirect nonspecific reaction.

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PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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CHEMOTHERAPY OF TUBERCULOSIS

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IF the proposition that "The continued chemotherapeutic advances in tuberculosis produce more problems than are solved" were debated by a group of internists, thoracic surgeons, pathologists, bacteriologists, roentgenologists and public health workers active in the field of tuberculosis, there is little doubt but that the proposition would be carried unanimously. The reaffirmation of basic pathologic concepts, the rapid improvement of surgical techniques, the discovery of a number of effective anti-tuberculous drugs and finally the virtual abandonment of many therapeutic procedures formerly employed in the treatment of this disease such as therapeutic pneumothorax or phrenic nerve crush have contributed to these problems. The past decade has witnessed more changes in the therapy of tuberculosis than probably any other disease during the same period of time. During the first 6 months of 1951 the titles of approximately 1220 articles dealing with the treatment of tuberculosis and other related problems are listed in the Quarterly Index Medicus. Many of the questions raised by the recent advances in chemotherapy are basic and fundamental and can be answered definitively only after the passage of many years. However, a few tentative conclusions may be reached at the present time. During the past 6 months several excellent review articles and editorials have appeared on this subject[15,46,57,96,120]. Another survey article may seem repetitious but it affords the opportunity to review a few basic clinical principles and to orient one's thoughts concerning the recent advances in chemotherapy. No attempt will be made to review the extensive recent foreign literature on the subject.

Purpose of Chemotherapy. In a recent discussion of surgical advances in the treatment of pulmonary tuberculosis[8] Amberson has succinctly stated:

"The primary purpose should not be to save time in the immediate future, although this usually is the patient's chief concern, but rather to bring the disease under such control that, after the necessary sacrifice of time, the chance of relapse will be minimized and the prospect of the patient's returning to an active and useful life will be reasonably well assured." This fundamental concept holds true also for the medical treatment of active tuberculosis and should be the basic premise determining the management of any case. Because of the often dramatic results following the short-time use of specific chemotherapy in the acute phases of the disease, this concept is too often ignored and too much emphasis is placed upon the short-term results alone.

Tuberculosis is a chronic infectious disease which, although occasionally presenting acute manifestations such as tuberculous pneumonia, meningitis, miliary disease or pleurisy with effusion, is more generally characterized by a protracted course with a marked tendency, even following adequate therapy, toward periods of exacerbations and relapse. It is the leading cause of death between the ages of 15 and 34, causes more deaths than any other infectious disease and in this country alone represents an economic loss of many millions of dollars. Although mortality has shown a consistent decline, the morbidity figures for 1950 were higher than those of 1940 by more than 20%[28]. This may be largely a relative increase as a reflection of more intensive case finding programs. In spite of these figures there is at the present time an unfortunate tendency to minimize the importance of tuberculosis in this country and the recent enthusiasm for antibiotics has provided considerable stimulus to this point of view.

The most common portal of entry for the tubercle bacillus into the human body is the respiratory tract so that pulmonary involvement is the most usual and most easily demonstrable manifestation of tuberculosis. The disease, however, is a generalized systemic one. Following the initial primary infection a post-primary hematogenous dissemination almost invariably occurs leaving quiescent foci of infection which for reasons not clearly understood may become reactivated under certain conditions of stress or strain. It is important to remember that when therapy is directed towards a roentgenographically demonstrable pulmonary lesion, there are other hidden undemonstrable foci of active disease. Tuberculosis differs from other common infections in that tissue necrosis is a distinctive feature even in the so-called "early" minimal pulmonary lesion visualized in an asymptomatic individual on routine chest roentgenogram[74]. When sufficiently developed to be seen by Roentgen-ray, the minimal lesion is well advanced pathologically, differing only quantitatively from advanced disease. Ulceration and sloughing with bronchial dissemination have already occurred. Employing sufficiently careful techniques a patent communication between the lesion and its draining bronchiole can almost always be shown. Healing of a tuberculous lesion anywhere in the body, either in the natural course of the disease or following therapy, does not often occur by complete resolution leaving an intact anatomical substrate. In any active tuberculous lesion there may be an exudative element which may resolve, but healing usually occurs through fibrous tissue proliferation and attempted encapsulation of residual foci caseation. Secondary irreversible anatomical changes are usually present. The planning of any therapeutic regimen must be based

upon the assumption that following prolonged rest, chemotherapy, or collapse measures residual foci of necrotic tissue harboring probably viable organisms are left behind following resolution of the reversible components. There is evidence, however, that these organisms, which may often be seen on smear, may not grow on culture media or cause tuberculosis when injected into experimental animals.

The evaluation of any therapeutic agent is difficult because of the natural tendency of this disease to heal. Chemotherapy, rest and other measures only hasten this natural tendency. The most important single factor to explain this tendency is the innate individual resistance of the host, an elusive factor which is difficult to evaluate since it cannot be measured in milliequivalents by a flame photometer or in millimeters of mercury by a manometer. None of the available effective anti-tuberculous drugs has been found to exert outside of the test-tube or experimental animal an unequivocally proven bacteriocidal effect. The various antituberculous drugs have a bacteriostatic effect in the human body, preventing the multiplication of susceptible organisms present in foci accessible to high concentrations of drug so that the normal defense mechanism of the body can hold the disease process in check. This factor of host resistance is intimately connected with the individual's socio-economic background, since with no other infectious disease is there as close a parallel between hunger, poverty, malnutrition, war and economic unrest as there is with tuberculosis. Dubos[29], has shown that the downward trend of tuberculosis mortality began long before the growth of the sanatorium movement, the organization of anti-tuberculosis associations or the introduction of collapse therapy. This is not due to any decreased virulence of the tubercle bacilli per man, but due to changes in the human host, the less resistant members dying off, the more resistant members remaining and resistance rising with improvement in the standards of living. It is gradually being noticed that the more acute fulminating types of tuberculosis are being replaced by the more chronic indolent types, indicating a more symbiotic relationship between the human host and the tubercle bacillus. There are fewer patients dying from tuberculosis but more patients with tuberculosis dying from other causes.

The Ideal Chemotherapeutic Agent. Following the discovery by Koch in 1882 that tuberculosis was an infectious disease caused by a specific organism, the search for a suitable antibacterial drug began and is still continuing. Florey[38] has listed the desirable properties for the ideal chemotherapeutic agent. It should be nontoxic and preferably bactericidal rather than bacteriostatic. It should reach high concentrations in the blood stream after parenteral or oral administration and perfuse in high concentrations into the serous cavities. It should be effective in the presence of pus and slough and should be recoverable in high concentrations from the centers of caseous necrotic foci. It should be able to diffuse into macrophages and epithelioid cells containing tubercle bacilli. Since long continued administration is necessary, it should not be carcinogenic. Although a substance of small molecular size is more diffusible than one of large molecular size, it would be possibly advantageous to have a substance of large molecular size which would pass through capillary walls of increased permeability only and then reach a selectively high concentration in the area of inflammation. It should be a substance against which bacterial resistance will not develop, since a pro-

longed antituberculous effect is desirable.

Although no antituberculous agent fulfilling all these criteria has yet been found, extraordinary advances have been made in this direction since 1938 when Rich and Follis[97] showed that the oral administration of sulfanilamide retarded to some degree the rate of development of experimental tuberculosis in guinea pigs. This finding led to the study of other related compounds. There are now many substances which have been found to have an antituberculous effect both *in vitro* and *in vivo* to varying degrees.

Available Antituberculous Drugs. Although Feldman[34] demonstrated that a number of the sulphones exerted a therapeutic effect in experimental tuberculosis, only two, sulphetrone and promizole, have been found valuable in the treatment of human tuberculosis.

Sulphetrone, a drug practically obsolete since the introduction of more efficacious and less toxic substances, was reported to have a therapeutic effect in chronic pulmonary tuberculosis but to have no effect upon the acute forms of the disease, in a series of 70 patients studied[6]. Although 40 patients observed over a 3-year period showed varying degrees of improvement which could be attributed to chemotherapy, the entire group developed secondary anemia and varying degrees of cyanosis. Other severe toxic reactions were frequent. The second drug in this group, promizole, has been used extensively by Lincoln and her coworkers at Bellevue Hospital in the treatment of childhood tuberculosis. When used alone this drug is ineffective in the treatment of tuberculous meningitis, although some therapeutic effect has been noted following its use in acute miliary tuberculosis[62,64]. The accepted value of promizole lies in its combination with streptomycin or dihydrostreptomycin in the treatment of children with miliary tuberculosis, tuberculous meningitis, or protracted hematogenous tuberculosis[63,65]. Dosage varies between 0.5 gm. and 1.0 gm. daily. The amount is adjusted until a blood level between one and 3 mg. per 100 cc. is reached 2½ to 3 hours after the usual dose. Therapy is continued for 2 to 3 years. The rationale of combined therapy is twofold: 1), to delay the development of bacterial resistance and 2), to improve the therapeutic results. The only commonly encountered toxic reactions, none of which in Lincoln's experience with combined therapy is sufficiently serious to necessitate discontinuing the drug, are thyroid gland enlargement and mild cyanosis. An elevated blood cholesterol is an inconstant finding. Cyanosis may appear within a few hours of the initial dose and may continue throughout treatment. It may become accentuated during febrile illnesses or when fluid intake is low. Reducing substances occasionally are present in the urine which may turn a cherry red or pink color.

Para-aminosalycilic Acid (PAS), the most important of a group of aromatic compounds, has now a significant place in the chemotherapy of tuberculosis. This drug, first introduced in Sweden by Lehman[59], was found to have the most active bacteriostatic effect *in vitro* among a group of compounds related to salicylic acid. An excellent review of this drug appeared in 1950[11]. Its action is bacteriostatic, probably by interfering with one of the essential metabolic processes of the tubercle bacillus, possibly one concerned with oxygen consumption. After absorption the drug diffuses freely throughout the body. The blood concentration after single oral doses, however, rapidly falls, so that the material must be administered frequently to maintain continuously high levels.

Eighty-five per cent of an administered dose can be recovered in the urine within 10 hours after administration. The development of resistant strains of tubercle bacilli occurs rather slowly. The chief toxic effects which are often troublesome and which in some patients may necessitate either decreasing the dosage or temporary or complete withdrawal of the drug are usually anorexia, nausea, and vomiting. Marked variations in patient's tolerance have been noted. A definite psychogenic element seems to play a part in some. Rashes and drug fever have been occasionally reported. Symptoms of salicylism have not been seen, even following prolonged use. In efforts to minimize the unpleasant gastrointestinal effects, several different preparations are on the market and patients intolerant of one may be found to tolerate another. The drug should not be administered on an empty stomach. Tolerance may sometimes be achieved by starting with low daily doses and gradually increasing them or by administering the drug on an intermittent basis. Intermittent treatment, however, has proven unsatisfactory[52] so daily use of the drug is recommended. The sodium salt of PAS causes fewer gastrointestinal reactions than the free acid. The usually recommended dose is the equivalent of 12 to 15 gm. daily of PAS. The sodium salt should be used cautiously in cardiac patients or in patients whose sodium intake should be low, since this amount of sodium salt contains approximately 5 gm. of sodium.

Although clinical studies have demonstrated the effectiveness of this drug when used alone[17,54,90], the bacteriostatic effects are only moderate. The usual role of PAS at the present time is its use in combination with either streptomycin or dihydrostreptomycin, not only to provide a synergistic therapeutic effect but also to delay the development of bacterial resistance to the latter drugs. The primary drawback of the drug is its gastrointestinal toxicity. In a recent attempt to reduce the severity and incidence of these disturbances, the calcium salt of PAS has been substituted for the sodium salt with considerable preliminary success[106]. The report of Boger and Pitts[13] that the use of Benemid retards the excretion of PAS without retarding the excretion of streptomycin may provide a means of reducing the side effects upon the gastrointestinal tract. Eight grams daily of PAS in combination with Benemid produced the same plasma concentrations as 12 gm. daily of PAS alone. At this dosage of PAS the side effects were considerably reduced. Further reports confirmed these findings[2,16,23]. However, a recent study[99] has failed to demonstrate any enhancement of the PAS blood levels following the concomitant use of Benemid, and further work on this problem is indicated. Although oral administration of PAS is most frequently employed, preparations suitable for either parenteral or rectal administration are now available.

The discovery of penicillin was followed in rapid succession by the introduction of a number of mold derivatives which were found both *in vitro* and *in vivo* to possess antituberculous properties. Several of these have little if any place in the treatment of clinical tuberculosis. Only those of clinical importance will be mentioned.

Terramycin was first demonstrated to have a significant bacteriostatic effect *in vitro* in 1950[49]. It was also shown to have a significant bacteriostatic effect in experimental tuberculosis[50]. The first extensive clinical studies with terramycin showed that when used alone the therapeutic effects of this drug were not impressive[122]. A most important observation,

however, was the fact that the emergence of strains of tubercle bacilli resistant to streptomycin appeared to be suppressed or delayed when the 2 drugs were given concomitantly[76,103,110]. Terramycin in an oral daily dose of 5 gm. given in combination with intermittent streptomycin prevents the emergence of streptomycin resistant organisms at the end of 120 days of therapy. The combination also compares favorably from the standpoints of toxicity and therapeutic effectiveness. Because of the high cost and relatively high incidence of unpleasant gastrointestinal reactions, current studies employing 2 gm. of terramycin daily are in progress. Terramycin is an available substitute for PAS when the latter cannot be used because of toxicity.

Viomycin, the most recent member of this group, was first introduced in 1950[48,91,116]. Considerable interest followed the publication of a series of articles pertaining to the *in vitro* and experimental use of this drug[7,32,37,51,55,89,115,127]. Clinical studies, however, have indicated considerable toxicity[125]. A small group of patients receiving daily doses of 30 to 75 mg. per kg. of body weight from 14 to 182 days; all developed albuminuria and cylindruria. Five of the group of 10 patients developed anorexia, nausea, weakness, lassitude, muscle cramps and paresthesias which were accompanied by striking electrolyte disturbances. These changes were a fall in serum potassium, calcium, phosphorus and chlorides with an increase in the carbon dioxide combining power of the serum, and were accompanied by the expected electrocardiographic abnormalities. Two patients developed overt tetany. Two others developed impaired vestibular function. Although the explanation of these electrolyte disturbances is obscure, it is suggested that they may arise from an increased excretion of these substances by the kidneys secondary to the nephrotoxic action of this drug. Further studies on the intermittent administration of viomycin[93] showed that although the incidence of clinical and laboratory toxicity is high, the changes are essentially minor, transient and reversible upon completion of therapy. Sufficient therapeutic effect has been noted upon both pulmonary and extrapulmonary tuberculosis to warrant further clinical investigation at lower doses and in combination with other drugs. It is possible that a role for viomycin may be found in its use in short courses of intermittent therapy when combined with either streptomycin or PAS. It might be developed as a substitute for streptomycin in streptomycin-resistant cases or when excessive toxicity to this drug is present. This drug is about to be released by the Food and Drug Administration for clinical use.

It is unique that streptomycin, the first of this group of mold derivatives to be discovered, should be the least toxic and exhibit the highest antituberculous activity of this entire group. The discovery of streptomycin in 1944 by Waksman and his coworkers[107] opened up a new era in the chemotherapy of tuberculosis. The first reports of the effect of this drug on experimental tuberculosis[35] and in clinical studies[47] are historic landmarks in the chemotherapy of infectious diseases. In the ensuing 7 years the effects of streptomycin have been studied in many thousands of cases of all types of pulmonary and extrapulmonary tuberculosis. Approximately 10,000 cases have been evaluated by the Veterans Administration alone. Probably no other antibiotic has ever been subjected to such exacting, well-coordinated and intensive critical scrutiny.

The usual method of administration of streptomycin and its reduction pro-

duct, dihydrostreptomycin, is by the intramuscular route. The drugs are not effective when given orally. There is no unequivocal evidence that either form has a bactericidal effect at the concentrations reached in clinical use. They diffuse easily into all serous cavities. They pass at higher concentrations across an inflamed than a normal meningeal membrane. Neither drug diffuses readily into areas of caseation necrosis, probably because of the relative avascularity of these lesions. Pus appears to have an unfavorable effect upon their bacteriostatic properties, possibly because of the depressant effect of an acid pH[1]. Their most effective use is in the treatment of fresh exudative reversible lesions before necrosis or irreversible fibrotic changes incident to healing have occurred. Both forms of the drug are excreted by the kidneys, so that some danger exists, more theoretical than real, of administering them in the presence of severe renal damage or failure. Dermatitis, eosinophilia and febrile reactions are occasionally seen but are relatively unimportant following the introduction of lower dosage regimens and elimination of impurities. Allergic reactions can generally be controlled through desensitization, by giving initial small doses and gradually increasing up to the optimum dose. The most serious toxic effects are neurological ones, involving both the auditory and vestibular branches of the eighth cranial nerve. This is a central, rather than peripheral effect, resulting from the unique and incompletely understood specific selective toxic effect of streptomycin upon the eighth nerve nucleus[118]. Tinnitus, vertigo, ataxia and hearing loss, ranging from a diminished acuity at higher tone frequencies to complete deafness, can all occur. These toxic effects were seen most frequently during the first years of streptomycin therapy when high doses of the drug were given routinely. Although the side effects upon the vestibular branch are usually reversible or may be compensated by other mechanisms, deafness may be progressive even after chemotherapy is discontinued and is more likely to be permanent than the toxic effects upon the vestibular branch.

It became readily apparent during the early studies of streptomycin that three closely related problems existed. The first was to determine the optimum dose and duration of treatment and to discover if combining streptomycin with another bacteriostatic drug provided any additional therapeutic benefit. The second problem was to find a way to diminish the incidence and severity of toxic reactions without compromising the therapeutic effect. The third problem was how to diminish or prevent the development of drug resistance, a phenomenon observed with disturbing frequency when high doses of streptomycin were used alone, especially in the therapy of advanced grossly cavitary disease in patients with large numbers of tubercle bacilli in their sputum. The existence of these problems has already been implied in the preceding discussion and has provided a potent motivating factor in the search for other effective antituberculous agents.

It is pertinent at this point, without becoming unduly involved in the still poorly understood complicated bacteriological aspects of the problem, to interpolate a few comments on this extremely important factor of drug resistance. Bacterial resistance does not necessarily depend upon previous contact with the drug, since naturally resistant strains of tubercle bacilli have been reported. There have been reports of the development of streptomycin-dependent strains[60,88]. The development of resistant organisms occurs genetically through mutations. Two

criteria are apparently necessary: 1) the substrate must be conducive to continued bacterial growth, and 2) there must be a selective suppression of sensitive organisms. The desirability of maintaining sensitivity is obvious, not only so that the patient's disease will show more response to chemotherapy, but also so that the patient will not become an even greater public health hazard by disseminating drug-resistant bacilli. Resistance may not always be permanent, since some months or years after its development sensitive cultures may occasionally be once more obtained if chemotherapy has been discontinued.

It has been argued that *in vitro* resistance does not necessarily correlate with *in vivo* resistance and that clinical improvement may continue even though resistant organisms are demonstrable. It is true that techniques used to determine resistance are not completely satisfactory, and that the recovery of resistant colonies does not mean that the entire bacterial population is necessarily resistant. The criteria for resistance have been rather arbitrarily defined. Further chemotherapy may be of value when tubercle bacilli are completely resistant to 10 mcg. of streptomycin per cc. of culture medium and even when the bacilli are partially resistant to 100 mcg. of streptomycin per cc. This observation, plus the fact that at the present time more than one effective antituberculous drug is available and that cross-resistance does not occur, has perhaps encouraged some workers to minimize the importance of resistance. However, there is sufficient correlation with clinical response to justify the use of any available means for maintaining bacterial sensitivity to the drug in question.

At the present time, the chemotherapy regimen providing a maximum therapeutic effect, a minimum of toxic reactions and the maximum suppression of the development of bacterial resistance is that combining 1 gm. of streptomycin every 2 to 3 days and PAS, 12 to 15 gm. daily[5,52,121]. This regimen is as effective as both drugs used daily, and more effective than both drugs administered every 3 days or alone. Drug resistance among positive cultures decreased to 17% after 120 days of therapy, after which time the low incidence of persistently positive cultures made sensitivity studies difficult. The mechanism by which combined chemotherapy retards the development of resistance is obscure. It may be related to the fact that organisms resistant to the effect of one of the drugs are still susceptible to the bacteriostatic effects of the other. On this intermittent combined regimen the development of toxic reactions to either or both drugs is slight, and rarely if ever indicates discontinuing chemotherapy prematurely[109].

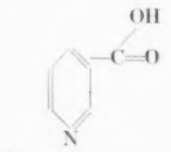
There is essentially no difference between streptomycin and dihydrostreptomycin from the viewpoint of therapeutic efficacy. However, there is some evidence to show that the incidence of deafness is higher following the prolonged use of dihydrostreptomycin than regular streptomycin, although the incidence of vertigo is less[24,80]. Some authorities feel that deafness occurs more often with dihydrostreptomycin hydrochloride than with the sulfate at high doses or that it may occur as a result of impurities in the particular preparations used[81]. A carefully controlled investigation to study the relative toxicity of streptomycin and dihydrostreptomycin, their relative therapeutic efficacy and any differences in the emergence of drug resistant organisms has recently neared completion[66].

The final group of substances found to have an antituberculous effect is the nicotinic acid derivatives (Fig. 1). The

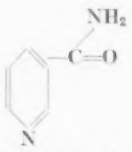
effect of nicotinamide on the experimental tuberculosis of mice was first reported in 1948[71], and was shortly afterward followed by an exhaustive study of other related compounds.

The first of these to undergo extensive clinical trials was Amithiozone (Tibione), a drug first synthesized in Germany by Behnisch[8]. This drug is a member of a general group of

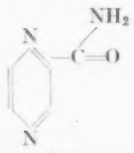
FIG. 1.—STRUCTURAL FORMULAS OF NICOTINIC ACID DERIVATIVES



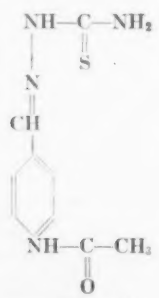
Nicotinic Acid



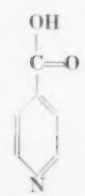
Nicotinic Acid Amide



Pyrazinamide (Aldinamide)

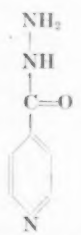


Amithiozone (Tibione)

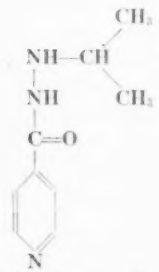


Isonicotinic Acid

Isonicotinic Acid Amide



Isonicotinic Acid Hydrazine (Nydrazid, Rimifon) (Isoniazid)



1-Isoniotinyl 2-Isopropyl hydrazine (Marsilid) (Iproniazid)

thiosemicarbasones and is only distantly related to nicotinic acid. Initial studies in experimental and clinical tuberculosis were reported by Domagk and others[27,75]. Using doses as high as 200 to 400 mg. daily, good tuberculostatic effects were described, although a high incidence of complications involving bone marrow, liver, and skin were noted. Anithiozone was first introduced into the United States in 1950[22]. Further clinical studies at doses of 200 mg. daily failed to substantiate the initial enthusiasm[83]. Only mediocre therapeutic results were noted when, in an effort to reduce toxicity the dosage was reduced to 100 mg. daily[20,108]. Attempts to defer the emergence of streptomycin-resistant strains of tubercle bacilli by combining Tibione and streptomycin are not encouraging[87]. It is doubtful if an important role will be found for this drug in the treatment of tuberculosis.

The second substance of this series, pyrazinamide, (Aldinamide) has a more promising future. Experimental studies[26,68] have shown that this drug possesses tuberculostatic activity lying between that of streptomycin and PAS. Preliminary clinical studies[126] indicate that on a dosage schedule of 350 mg. given 4 times the first day and 700 mg., 4 times daily for a subsequent course of 42 days, considerable symptomatic improvement was noted in a group of 43 patients. Because of the far advanced fibrotic cavitary type disease in the majority, little roentgenographic change was noted. Toxic reactions were mild. Gastrointestinal complaints were few. The most important side effects were joint pains, eosinophilia, cardiac palpitations, and jaundice. An unfortunate feature was the rapid emergence of resistant strains of tubercle bacilli which developed in all 12 patients whose bacilli were tested for sensitivity before and after treatment. Further studies using longer courses of the drug and in combination with other tuberculostatic agents are in progress.

The most effective and least toxic members of this series at the present time are the hydrazine derivatives of isonicotinic acid, which, at the time of their introduction in 1952, were given such unfortunate and premature publicity by the lay press. Benefiting from earlier experiences, investigators have accumulated almost as much information concerning these substances in the past year as they did in several years of studies with streptomycin.

In a paper published in 1951[42], Grunberg and Leiwant described the tuberculostatic effect of the thiosemicarbasone of isonicotinaldehyde on experimental tuberculosis. Further laboratory work resulted in the synthesis of isonicotinic acid hydrazide and its isopropyl derivative. Isonicotinic acid hydrazide was discovered independently by research workers at Hoffman-LaRoche and E. R. Squibb to have a marked antituberculous effect in experimental animals infected with both human and bovine strains of *Mycobacterium tuberculosis*[10,44]. Preliminary findings were confirmed by further investigations[43,117,128]. These substances proved to have a greater antituberculous effect than any of the previously discovered chemotherapeutic agents including streptomycin. There was some evidence to suggest that their *in vitro* action was a bactericidal one. The isopropyl derivative has not yet been released by the Food and Drug Administration for clinical use.

The first clinical studies were reported from Sea View Hospital on Staten Island[14,40,41,100,101,102,111,112]. The majority of patients studied had received prolonged courses of combined streptomycin and PAS. Many had shown no response to previous treatment and were classified as clinically

"hopeless" with far advanced bilateral cavitary tuberculosis. The initial reports were based upon a series of patients observed for periods varying between 4 and 15 weeks. All patients had persistently positive sputum and widely open cavities. On doses of 2 to 4 mg. per kilogram of body weight of isonicotinic acid hydrazide (henceforth the newly adopted general name isoniazid will be used exclusively) daily and on doses of 2 to 10 mg. per kilogram of body weight of the isopropyl derivative (iproniazid) daily, within 2 to 3 weeks fever, malaise, cough, expectoration and other signs of toxicity cleared "with a rapidity, a certainty and to a degree which we have never observed in other chemotherapeutic or antibiotic agents"[102]. Marked weight gains and a remarkable recovery of appetite were noted. Food consumption by the patients was reported to have increased by 50%. Sputum became negative on smear in approximately 25% of the patients and in an additional 28% became only intermittently positive with a marked reduction in the Gaffky count. This phenomenon occurred even if cavities remained open. Fifty per cent of the cases showed little roentgenographic change. In many instances, obviously irreversible anatomical changes had occurred, so that dramatic roentgenographic changes could not be expected. In the remaining patients there was some resorption of the exudative components and in a number of cases cavity closure or marked reduction in size was reported. Marked improvement was also noted in extrapulmonary tuberculous lesions, which have been the subject of separate reports[14,40,41]. In addition to the general systemic effect, in patients with orthopedic lesions persistently positive washings from draining sinuses became negative after 4 weeks of therapy, inflammatory reaction and drainage decreased, and healing accelerated. Renal symptoms showed marked improvement, although no bacteriological reversion to negativity has been noted. A particularly marked improvement was noted in the symptoms of tuberculous laryngitis and enteritis.

The preliminary clinical studies showed little therapeutic difference between isoniazid and its isopropyl derivative in the doses employed. No clinical evidence of bacterial resistance was encountered. With streptomycin, however, a gradual return of symptoms with an increased bacillary count have been noted in patients with massive caseous pneumonic tuberculosis under prolonged therapy[111].

A more recent report[112] deals with a total of 101 patients treated with iproniazid from 3 to 7 months in daily divided doses of 4 mg. per kilogram, and 65 patients treated with isoniazid from 2 to 5 months in divided daily doses of 4 to 8 mg. per kilogram. Contrary to the earlier reports, it was found that iproniazid had a much more certain predictable and marked effect upon systemic manifestations. This has been confirmed in the most recent report from Sea View[101]. Although toxic symptoms showed a prompt response, favorable Roentgen-ray changes, although occasionally occurring within 2 to 3 months, did not occur in significant numbers until the beginning of the sixth month of therapy. This held true for either drug.

The work at Sea View was followed shortly after by reports of other clinical studies from the New York Hospital[33] which were begun independently without any knowledge of the Sea View investigations. Isoniazid was given in daily oral doses of 3 mg. per kilogram of body weight for periods varying from 4 to 16 weeks to a group of patients with moderately or far advanced pulmonary tuberculosis, the majority of whom had received pre-

vious long courses of streptomycin and PAS and whose sputum no longer contained streptomycin sensitive organisms. The drug was rapidly absorbed and rapidly excreted in the urine, confirming experimental work indicating that the maintenance of constant blood levels requires multiple doses[105]. Appreciable concentrations appeared within 3 hours of a single oral dose in the cerebrospinal fluid of 9 patients, 5 of whom had active tuberculous meningitis at the time of study. Since this group of patients was under study for a shorter period of time than the Sea View group, the New York Hospital investigators felt that their results provided no basis for making any positive statements concerning the therapeutic value of isoniazid.

Prior to the clinical studies, the toxicity of these compounds had been extensively studied in experimental animals[9,104]. The MLD in mice is approximately 144 mg. per kilogram, in dogs about 50 mg. per kilogram of body weight. Single doses in the acutely toxic range induced signs of central nervous system stimulation terminating in death from respiratory failure. In mice and dogs, the isopropyl derivative is less toxic than the parent compound. The converse is true in rats and rabbits. Prolonged administration of the drugs in high doses to dogs produced a fall in hemoglobin and erythrocyte count, occasionally accompanied by jaundice and hematuria.

Untoward side effects noted in clinical studies[113] included symptoms suggesting central nervous system stimulation (hyperactive deep reflexes, leg twitching and insomnia) and symptoms of modified autonomic activity, such as dryness of the mouth, sphincter disturbances and constipation which may be sometimes modified by the use of prostigmine. Muscle weakness was common. Vertigo and postural hypotension were occasionally noted. No serious toxic effects on liver, kidney or bone marrow were reported. A slight drop in hemoglobin sometimes occurred. Transient minor hesitancy of urination and increased sexual stimulation were noted in some of the patients treated for genito-urinary tuberculosis. No evidence of gastrointestinal irritation appeared. Except for a moderate eosinophilia noted in a number of instances, no allergic reactions developed. Evidence of renal irritation was minimal. On rare occasions reducing substances were present in the urine. Pulmonary hemorrhages have been reported, but in view of the high incidence of this complication of pulmonary tuberculosis, their appearance is probably coincidental. Autopsies on 2 patients who died while on therapy failed to show any evidence of toxic effects. Experience gained from more prolonged study[101,112] indicates that side effects are more common and more clinically significant with iproniazid, although qualitatively the same. At dosage levels of 4 mg. per kilogram, these side effects are minor and rarely if ever necessitate termination of chemotherapy or reduction in dosage. Prolonged administration at higher doses may be followed by excitable behavior, convulsions or coma. Such a case terminating fatally has recently been reported[36]. These serious central nervous system side effects are more common in elderly patients, patients with unstable personalities, and patients with histories of previous psychotic episodes or convulsive disorders. These effects, which may be aggravated by the use of adrenergic drugs, indicate careful observation in patients in uremia or in whom renal excretion is impaired[58]. The precaution of doing blood levels may be necessary in these circumstances. In 2 cases under prolonged therapy with iproniazid, surgical anesthesia caused severe reactions.

These side effects tend to appear early in the course of therapy, to persist for several weeks and then, with the exception of a sustained hyperreflexia, to subside. An interesting observation is the development of a "withdrawal syndrome" following discontinuation of therapy after prolonged administration. This consists of irritation, restlessness, excessive dreaming, headache, lethargy, vertigo and slight nausea. This syndrome is inconstant, appearing more frequently following iproniazid than isoniazid, develops 24 to 48 hours after cessation of therapy and may last approximately 10 to 14 days. In contrast with the Sea View observations, no side effects were noted by the New York Hospital workers. This discrepancy is difficult to explain. Further longer-term studies of toxicity are in progress.

The development of bacterial resistance to these isonicotinic acid derivatives was anticipated early in their investigation. The first well documented report of the development of bacterial resistance came from Trudeau Sanatorium[114]. Definite evidence of increased bacillary resistance was encountered in 3 of 6 patients with chronic cavitary pulmonary tuberculosis after 7 weeks of treatment. In one patient resistance developed after only 26 days of therapy. The appearance of resistant strains was followed closely by a rise in the bacillary count of the sputum.

Several laboratory studies have also indicated the rapid development of resistance[84]. Bacilli with a 5-fold increase in resistance to iproniazid and a 16 to 4000-fold increase in resistance to isoniazid have been obtained by serial passage in media containing these drugs. Resistance has been seen to develop 1000 times as rapidly as resistance to streptomycin. Cross resistance between streptomycin and the isonicotinic acid derivatives does not occur, but definite cross resistance occurs between isoniazid and the isopropyl derivative. Resistance develops in single rather than multiple steps. The drug resistant variants may lose the acquired resistance almost as rapidly as it developed when cultured in a drug-free medium. A significant finding reported by Middlebrook[84] was the failure of resistance to develop when bacilli were grown in tubes of media containing both isoniazid and streptomycin. No tubercle bacilli resistant to either isoniazid or streptomycin were encountered in cultures exposed simultaneously to therapeutic concentrations of the 2 drugs, although strains resistant to both have been obtained by successive exposure to these substances. That resistance is not always acquired but may exist in strains which have had no previous contact with isoniazid was reported by Hobby and Lenert[84] and also by independent studies from the Mayo Clinic[56].

Extensive clinical studies on the development of bacterial resistance are currently in progress. Preliminary reports from the Veterans Administration[94] indicate that among 600 patients treated with 150 mg. of isoniazid daily, 5.5% of 417 cultures were resistant at 2 to 6 weeks of therapy, 91.4% of 159 positive cultures were resistant at 7 to 10 weeks of therapy and 10.0% of 80 persistently positive cultures were resistant at 11 to 14 months of treatment. Most of the resistant cultures were from patients with far advanced cavitary disease. Meade[72] in a study of 44 cases reported an 85% incidence of resistance at the end of 10 weeks of treatment among 14 patients whose sputum remained positive. In a later report from the Veterans Administration[95] Hinshaw states that on a daily regimen of 200 mg. of isoniazid, 10% of patients became resistant within the first month of treatment, 50% within 2 months and that at 3 months at least

90% have resistant organisms. These reports indicate a definite limitation to the use of isoniazid alone. Among Meade's patients who had completed at least 16 weeks of either isoniazid or iproniazid therapy, deterioration either from a roentgenographic or bacteriologic standpoint developed in 30. The majority of relapses appeared after the patient's organisms had become resistant. Eighty per cent of this group, however, had far advanced disease and a generally poor prognosis.

Further clinical studies on resistance come from Great Britain[73]. One hundred and seventy-three patients with various forms of pulmonary tuberculosis were treated with 200 mg. of isoniazid daily. Drug toxicity and general therapeutic results were similar to observations reported elsewhere. Resistance to isoniazid developed in 11% of the cases at the end of the first month of treatment, in 52% at the end of the second month and in 71% at the end of the third. The absence of roentgenologic improvement could be correlated with the emergence of drug resistance.

It was previously noted[38] that the ability to diffuse into phagocytes is one of several factors which determine the effectiveness of an antituberculous drug. Reports from the Rockefeller Institute[119] indicate that the concentration of streptomycin required to inhibit the intracellular growth of tubercle bacilli is approximately 100 times greater than that required to inhibit extracellular growth. In contrast no difference was noted between the minimal inhibitory concentration of isonicotinic acid hydrazide for either intracellular or extracellular bacilli. These observations were confirmed by Mackaness and Smith[67] who found that isoniazid differs from most other antituberculous drugs in its ability to diffuse freely into cells and exert its full bacteriostatic effect intracellularly.

So many variables enter into the clinical picture of tuberculosis that it is extremely difficult to evaluate the comparative effects of different drugs, combinations of drugs or optimum dosage regimens. Among these variables are age, sex, and race. Others are the extent of disease, its acuteness or chronicity, the duration and amount of irreversible anatomical change, the number and virulence of the infecting organisms and most important of all, the innate host resistance. Another difficulty is in the interpretation of roentgenographic changes which may be read differently by equally competent observers, especially when only minor grades of changes occur. Interpretation may be influenced by technique, subconscious prejudice, fatigue and a host of other variables. The same film may be read differently by the same observer at different times.

Because the course of untreated acute miliary tuberculosis or tuberculous meningitis is generally fatal within a predictable short period of time and because in the former manifestation of the disease there is probably a minimal disagreement in Roentgen-ray interpretation, the initial report of the treatment of miliary and meningeal tuberculosis with isoniazid is of considerable interest[19]. Ten patients with uncomplicated miliary tuberculosis were treated with isoniazid, with few exceptions receiving approximately 10 mg. of isoniazid per kilogram of body weight daily for the first week of therapy. The dose was then usually decreased to between 5 and 7 mg. per kilogram. In every instance, therapy was followed by remission of all clinical evidence of infection and by regression or complete disappearance of the miliary densities. With regard to rate of defervescence and roentgenographic clearing no difference was noted with a previous group of cases of acute miliary tuber-

culosis treated with 3 gm. of streptomycin daily[70]. However, no relapse occurred in the group of patients receiving isoniazid, in contrast to several patients whose disease relapsed while streptomycin therapy was continuing. During a comparative period of time several patients with acute miliary tuberculosis developed meningitis while receiving streptomycin. This complication was not noted in the isoniazid treated group.

Three of the 10 patients with meningeal tuberculosis treated with isoniazid alone died during the first week of therapy. All subsequent patients with meningitis in addition received streptomycin intramuscularly. The early results indicate that isoniazid may have considerable value in the therapy of tuberculous meningitis, although it will probably never be used alone. Its use may eventually eliminate the necessity of intrathecal streptomycin, a route of administration which is extremely traumatic to the patient over long periods of time and frequently accompanied by serious complications.

Following the clinical and laboratory demonstrations of the marked antituberculous activity of these drugs, a problem of immediate importance and pressing interest was a comparison of their therapeutic effect with that of streptomycin and dihydrostreptomycin. This comparison is made difficult by the lack of knowledge concerning optimum dosage, toxicity, and optimum duration of therapy. It will take several years before the answers to these questions are realized. It seems well established that *in vitro* studies and studies in experimental tuberculosis have shown that these drugs, in comparative doses, are as effective, if not more so, than streptomycin. For reasons already mentioned, clinical studies are extremely difficult to evaluate. Conclusions are often reached by "impression" alone without adequate statistical evidence or well established concurrent control groups, which are essential for the accurate appraisal of different therapeutic agents. As Hart has said[45], ". . . it may be stated that careful objective assessment, based on previous experience with similar types of cases as a standard, should, with rigid safeguards, be adequate to demonstrate whether a new drug gives either benefit or no benefit, provided its action is more than slight. On the other hand, the inclusion of a matched control series, studied concurrently to permit comparisons having statistical validity, would seem imperative for a precise evaluation of a new drug's possibilities, limitations, and the degree of permanence of its benefit."

The initial reports from Sea View Hospital on the short term effects of treatment with isonicotinic acid derivatives are encouraging, but should be accepted with reservations until confirmed elsewhere. The reports of the voracious appetite of many of these patients should be tempered by the realization that many of these individuals had previously been receiving PAS with or without artificial pneumoperitoneum, both of which may be severe stimuli to anorexia. The reports of definite cavity closure appear premature, since it is well known that apparently closed cavities may often later reopen after treatment is discontinued and that tomographic studies and examinations of resected or necropsy specimens will show residual cavities not apparent upon routine roentgenographic examination. The observation that all patients showed some degree of therapeutic response[111] has not been substantiated by other studies[33,72,94,95]. Relapses and exacerbations of disease while under treatment with the isonicotinic acid derivatives have been reported. These discrepancies may possibly be partly explained by the different types of dis-

ease under therapy. The most recent conclusion of the Sea View group is that short term results indicate the superiority of iproniazid over streptomycin alone or in combination with PAS. It is felt that comparisons with isoniazid cannot be made since the optimum dosage of this drug has not yet been definitely established, but that in doses of 4 to 8 mg. per kilogram of body weight it is at least equal to streptomycin alone or in combination with PAS.

The first controlled short-term clinical study on comparative therapeutic effects of streptomycin, PAS and isoniazid was recently completed in Great Britain[78]. In this series, 173 patients received 200 mg. daily of isoniazid, and 158 were treated with one gram of streptomycin daily and 20 gm. of PAS. At the end of 3 months of therapy there was more general improvement on isoniazid than on the streptomycin–PAS combination, although the difference was not great. Weight gain averaged 11 pounds for the former and 6 pounds for the latter group. Sixty-six percent of the streptomycin–PAS treated patients showed Roentgen-ray improvement compared with 56% of the isoniazid group. In a group of patients with acute rapidly progressive disease of recent origin, moderate or marked improvement was seen in 37% of the streptomycin–PAS treated cases and in 40% of the isoniazid treated patients. Roentgenographic spread occurred in one patient treated with streptomycin and PAS and in 10 patients receiving isoniazid. The proportion of cases becoming bacteriologically negative on culture before the end of the second month was 26% for the streptomycin–PAS group and 23% for the isoniazid group. The conclusion reached by this study is that for short-term results isoniazid is no more effective in the doses used than the combination of streptomycin and PAS.

Controlled studies are also in progress from the Veterans Administration[94]. Comparisons at 2 to 6 weeks and 7 to 10 weeks of therapy showed no significant advantage in a group of patients treated with 150 mg. of isoniazid daily (probably a suboptimum dose) compared with a group of patients receiving streptomycin and PAS. The difference in incidence of sputum conversion by smear was not statistically significant, but it was noted that the percentage of conversion continued to rise with the more prolonged treatment with streptomycin and PAS and remained unchanged in the patients receiving isoniazid. At least one hospital contributing to this preliminary report felt that the combination of streptomycin and PAS was definitely superior to isoniazid alone.

Present studies are now in progress to determine if the conclusions based upon short-term studies are substantiated following prolonged administration of these compounds. Short-term results may differ significantly from long-term observations.

Following the *in vitro* demonstration of a synergistic action between streptomycin and isoniazid[53], clinical studies were begun to determine the therapeutic activity of the drugs used in combination. Preliminary studies have been reported by the Public Health Service[78]. The following regimens were followed: A) Streptomycin-PAS, 1 gm. streptomycin daily plus 10 to 12 gm. PAS daily; B) Streptomycin-Isoniazid, 1 gm. streptomycin twice weekly plus 150 to 300 mg. isoniazid daily; C) Isoniazid, 150 to 300 mg. daily alone. No definite evidence was present at the end of 3 months to indicate one regimen materially better than any other. At the end of 20 weeks, however[79], a significant superiority in roentgenographic improvement was noted in patients who received isoniazid alone or in combination with streptomycin.

Clinical and laboratory comparisons were less marked. Roentgenographic deterioration occurred in only 13.4% of the streptomycin-PAS group, 8.2% of the streptomycin-isoniazid patients and in 10.4% of the isoniazid series.

Early studies[31] have shown that the emergence of bacterial resistance during daily isoniazid therapy appears to be markedly delayed by the concomitant administration of intermittent streptomycin and further studies along this line are proceeding. Studies are also proceeding to determine if the combination of isoniazid-PAS delays the emergence of drug resistant strains.

INDICATIONS FOR CHEMOTHERAPY. Since the patient suspected of having active tuberculosis is being committed to many months of therapy, it is of fundamental importance that every possible attempt be made to confirm the clinical evidence with either bacteriological or pathological studies before instituting chemotherapy. It is unwise to start chemotherapy as a diagnostic test. Although the isonicotinic acid derivatives have been found to have an antibacterial effect specific for the tubercle bacillus alone, streptomycin is effective against a number of different unrelated organisms. Diligent repeated sputum examinations will generally reveal the tubercle bacilli in cases of untreated active pulmonary tuberculosis. Since in the acute exudative type of disease irreversible necrosis may occur within a relatively short time, attempts to recover the organism should not be unduly delayed. A serious handicap is the fact that several weeks are necessary before the organism is demonstrable by cultural techniques.

In the early days of chemotherapy because of the double danger of streptomycin toxicity and bacterial resistance, it was felt that chemotherapy should be given in short courses and reserved either to cover surgical procedures or for patients severely ill, with acute caseo-pneumonic disease, with acute miliary tuberculosis or tuberculous meningitis. During the past 3 years following the introduction of several effective anti-tuberculous drugs and the evaluation of combined intermittent regimens, concepts concerning the indications for chemotherapy have changed considerably. As suggested by Bogen and Oatway[12], it is now rational and logical that all patients with active tuberculosis, pulmonary or extrapulmonary, should receive chemotherapy in combination with bed rest and other well established therapeutically sound procedures. This philosophy has gradually received increasingly wide support. It includes the treatment of types of active tuberculosis which hitherto had been given a relatively favorable prognosis when treated with bed rest alone. These manifestations include active lymph node tuberculosis, cases of acute tuberculous pleurisy with effusion and cases of active minimal pulmonary tuberculosis. Because of the relatively high proportion of patients in whom an acute tuberculous pleurisy with effusion is part of protracted progressive hematogenous tuberculosis and because approximately 25% of this group will later develop active pulmonary tuberculosis, the use of chemotherapy seems amply justified in this situation in efforts to prevent these later complications and to hasten resolution of the acute process. It has always been recognized that the optimum and most strategic time to treat tuberculosis is in its early minimal stage when there is a maximum of reversible exudation and a minimum of irreversible damage. Although short-term good results have been seen in the treatment of minimal pulmonary tuberculosis on bed rest alone, the high percentage of late relapses[77] indicates that the results even in the optimally treated patients are far from satisfactory. It was noted early[45] that the

prime objective of chemotherapy should be to find a drug or combination of drugs suitable for the treatment of minimal tuberculosis and since this objective has now been reached, there seems little justification for withholding chemotherapy in the treatment of minimal disease. It will take 5 to 10 years, however, before an accurate evaluation of this concept can be reached.

The indications for chemotherapy have been extended by some to include its use in individuals with a recent documented conversion of tuberculosis sensitivity from negative to positive, even though a primary lesion may not be demonstrable by Roentgen-ray[82,124]. This concept, however, has not yet received widespread support, although one can argue that it is based upon a logical premise.

The indications for chemotherapy in active primary disease in children are more restricted. Despite Lincoln's report that 23% of 622 patients who had primary tuberculosis as children subsequently died of this disease[61], children with active uncomplicated primary tuberculosis do not receive chemotherapy on her service[65], neither do patients with active endobronchial disease or those with minimal chronic pulmonary tuberculosis. There was no evidence to suggest that streptomycin prevented the development of complications, hastened resolution of the primary lesion, or accelerated healing of the endobronchial disease. The explanations of these observations is obscure at the present time. The high death rate from subsequent tuberculosis suggests that a long term well controlled study of the problem is indicated.

Duration of Chemotherapy. In the early days of streptomycin, it was recommended that the duration of therapy should generally not exceed 42 or 60 days[123]. Although no definite agreement now exists about how long chemotherapy should continue once begun, the evaluation of intermittent combined regimens indicates that maximum therapeutic benefits are achieved only after prolonged therapy. As recently as 1951, however, it was stated that [21] "it remains to be demonstrated conclusively that treatment may be continued for as long as one year with continued benefit, but there are some indications that prolonged drug therapy may be justified occasionally when the clinical need continues to exist, and provided that other medical, surgical and environmental therapeutic aids are being intelligently and aggressively brought to bear upon the problem simultaneously." A little over a year later, the same committee (1) reported that when combined intermittent chemotherapy is employed "treatment should be continued for at least 6 to 12 months in every case and that those patients with the more serious types of tuberculosis should be treated 18 to 24 months, possibly longer." D'Esopo and his associates[25] were the first to demonstrate the excellent results and low incidence of relapse when pulmonary tuberculosis is treated with chemotherapy for a year or longer without interruption. It is now generally agreed that antimicrobial therapy for any form of active tuberculosis should be continued for a minimum of 12 months and in many instances longer. Treatment should be continued well beyond that time at which clinical activity is thought to cease, since it is well known that there is a poor correlation between clinical and pathological criteria of active disease. It is only if one keeps oriented regarding the basic pathological processes involved that a logical and rational course of treatment can be followed. The indications for discontinuing chemotherapy are admittedly arbitrary. It will take many years before the incidence of later relapse can be

correlated with chemotherapeutic regimens of varying duration, especially when combined with the excision of residual caseous foci, the possible source for bronchogenic dissemination at a later date. There is no reason to believe that the isonicotinic acid derivatives will in every way decrease the indications for long-term continuous therapy in combination with surgery, and every reason to believe that what has been learned concerning the long-term combined intermittent use of streptomycin and PAS will apply to these drugs also.

Drugs and Dosages of Choice. Among the many problems posed by chemotherapeutic advances in tuberculosis, the most pressing ones pertain to the choice and optimum dosage of the various available effective antibiotics. Studies of the synergistic action and development of bacterial resistance have clearly shown that none of these drugs should ever be used alone. This seems particularly true for the isonicotinic acid derivatives[39]. It would also seem logical, that the 2 most effective compounds should not be used together except in exceptional circumstances, but that one should be held in reserve in case bacterial resistance or drug toxicity develops to the other. For the average case of streptomycin sensitive pulmonary or extrapulmonary active tuberculosis, the therapeutic regimen of choice at this time still remains streptomycin, 1 gm., 2 or 3 times weekly, combined with 12 to 15 gm. daily of oral PAS. If the patient is severely ill with far advanced pulmonary disease, severe tuberculous pneumonia or extensive hematogenous tuberculosis, streptomycin should be given in doses of 1 gm. daily, which may be later reduced when the clinical situation improves. For the average case of chronic active streptomycin-resistant tuberculosis, the regimen of choice is isoniazid probably combined with 12 to 15 gm. daily of PAS. If the patient cannot tolerate PAS in any form or in even small doses when given in combination with Benemid, Terramycin should be used in its place. Probably the only indication for using streptomycin and isoniazid simultaneously is in the treatment of tuberculous meningitis, acute miliary tuberculosis, or some other equally desperate clinical situation. Since the prognosis of even treated tuberculous meningitis is so poor, it is felt that isoniazid and PAS should be given concurrently with daily intramuscular and intrathecal streptomycin, the latter in doses of 50 to 100 mg.

There is no question but that clinical studies may eventually prove the inferiority of the combination of streptomycin and PAS either for long- or short-term results or both. The isonicotinic acid derivatives are far cheaper, much less toxic and much easier to administer than streptomycin and may eventually prove to be therapeutically superior. This will take several years of well controlled studies to demonstrate. However, much more is known concerning the limitations, potentialities and efficacy of the streptomycin-PAS combination, and until additional studies have accumulated the routine clinical use of the isonicotinic acid derivatives should probably be reserved for the indications noted above. The only indication for dihydrostreptomycin is in patients unable to tolerate streptomycin because of allergic or sensitivity reactions in whom attempts at desensitization have been unsuccessful.

The Role of Chemotherapy. It was appreciated early in the investigations with streptomycin that chemotherapy provided no panacea or ready solution for the many difficult therapeutic problems presented by this disease. The most important role of chemotherapy in the treatment of tuberculosis is its proper integration with other well ac-

cepted types of therapy, particularly surgery and bed rest. Rest, both for the local disease and for the individual as a whole, both physical and mental, is still the basic form of therapy for active tuberculosis which has withstood the test of time. It would be disastrous to disregard prematurely this basic therapeutic principle because of the recent enthusiasm aroused by the often dramatic short-term effects of chemotherapy upon acute active disease. There appears to be a growing tendency to treat tuberculosis on an ambulatory basis: in the occasional circumstance this may be a wise and necessary compromise, but definite evidence of the wisdom of this trend is not yet forthcoming. There is also an increasing inclination to treat patients at home rather than to recommend sanatorium or hospital care. This is often dictated by economic reasons over which physician and patient have little control. In a sanatorium, however, there is often an environmental and group psychology which is more conducive to rest and makes the necessary physical restrictions more acceptable to the patient than at home where temptations and distractions are greater. It should be admitted, however, that for some patients the separation from their home environment, families, and acquaintances may be so unacceptable that, as with bed rest, a compromise may not only be necessary but wise.

Along with the coordination of bed rest and chemotherapy, the proper timing of these measures with clinically indicated surgical procedures is of marked importance. Prior to commencing specific treatment the therapeutic course should be planned ahead as much as possible, preferably through the joint efforts of the internist and surgeon[85]. Any manifestation of active tuberculosis is a potential surgical problem and chemotherapy should not be begun simply to see what it will accomplish. The clinical indications, the clinical-pathologic rationale, the proper timing and integration of surgical procedures have been admirably presented by Amberson[3]. The present concept of long-term chemotherapy and bed rest for 8 to 12 months before surgery is a far cry indeed from the early recommendations that surgical therapy be instituted within a few months after chemotherapy is begun[98], that the optimum time for pulmonary resection might be within the first week of streptomycin therapy and that chemotherapy might be necessary for only 3 to 4 months postoperatively[80]. Chemotherapy should supplement rather than supplant other types of treatment. The future of chemotherapy in the treatment of tuberculosis is bright but its use should not be exploited or preclude the application of other therapeutic principles. Undue emphasis upon chemotherapy in disregard of basic pathologic fundamentals is not a realistic approach. The most important single principle stated in 1951 by the American Trudeau Society[21] that "drug therapy alone is not adequate treatment for tuberculosis" is still true in 1953. Despite the high current enthusiasm for the isonicotinic acid derivatives, there is no ground for the belief that these drugs in any way should alter or modify the basic therapeutic fundamentals of tuberculosis. If they should, these are indeed "anxious times in tuberculosis[69]. There is no real basis to think that periods of hospitalization may be shortened or that there is a decrease in the need of hospital beds for tuberculous patients. Actually, hospitalization has been prolonged in the cases of those patients whose course would have been rapidly fatal without the help of chemotherapy. The more extensive use of surgical procedures resulting from the favorable effects of drug therapy have also resulted in greater demands upon hos-

pital facilities. However dramatic the effects of chemotherapy may be in acute tuberculosis, the real problem of tuberculosis lies in its chronic and subacute forms. The disease is caused by an organism with a singular ability to adjust itself to a hostile environment and with an almost perfect adaptation to its host as an obligatory parasite.

One of the major threats to the effective application of chemotherapy lies in the failure to realize that chemotherapy is only one of the weapons presently available to treat tuberculosis[18]. Even more emphasis should be placed upon the case findings of early minimal tuberculosis where chemotherapy may prove most valuable. The results do not justify a decrease in funds for tuberculosis control programs or the abandonment of proven effective control methods[92]. Chemotherapy has not decreased the need for rehabilitation services or the need for improvement of social economic and nutritional factors which so influence the course of tuberculosis. A proper perspective must be maintained regarding the limitations as well as the importance of chemotherapy. There are as yet no short-cuts in the treatment of active tuberculosis. The problem of tuberculosis can probably not be solved by attempts at its eradication through chemotherapy. A more rational approach has recently been expressed by 2 eminent authorities in the field of tuberculosis, one a clinician, the other a bacteriologist, both of them recipients of the National Tuberculosis Society's "Trudeau Medal". In a discussion of antibacterial agents Amberson has recently written concerning the tubercle bacillus[4], "Its inroads may be checked and its territory confined, but to look for its extermination would be to ignore its tenacity of life and the consistency of its behavior. It would be wiser by far to plan for its long survival, to assume its undeviating parasitism, to anticipate its readiness to destroy the defenseless and hence, to maintain defenses permanently and well." In similar vein, Dubos has written[30], "Tuberculosis will be conquered only when man has learned to function according to a physiological way of life that renders him more resistant to tubercle bacilli and when he has created a social environment that protects him from exposure to infection." Looking about us with these thoughts in mind, it is obvious that there remains much to be accomplished.

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ADDENDUM. Since this paper was completed several significant clinical and laboratory studies on the chemotherapy of tuberculosis have been reported which should be mentioned to bring this essay up-to-date. The reader is referred to 2 excellent summary articles which have appeared during the interim, one by Tucker[23] analyzing the results of the cooperative investigation of the Veterans Administration, Army and Navy, during the years 1946 and 1953 and a second by Tempel and co-workers[22] summarizing the results obtained in a series of approximately 1300 tubercular patients treated with various combinations of chemotherapeutic drugs during the same period of time.

The study to evaluate the therapeutic effectiveness and relative toxicity of streptomycin and dihydrostreptomycin was recently concluded and reported by Lyght and Hawkins[15]. In over-all therapeutic efficacy the 2 drugs were not found to be measurably different in a study of 435 individuals completing a basic 4 months of chemotherapy, 213 on streptomycin and 222 on dihydrostreptomycin. This controlled study confirmed the previously held impression that streptomycin is more toxic for the vestibular system and that dihydrostreptomycin is more likely to cause auditory loss. Vestibular toxicity tended to occur early in the course of therapy; auditory toxicity tended to occur late, even after chemotherapy was discontinued.

Clinical loss of hearing, however, was comparatively rare and in the majority of patients the loss was detectable only through audiometric means. Streptomycin more frequently caused allergic reactions than dihydrostreptomycin.

In efforts to reduce the incidence of eighth nerve damage experimental studies with Distrycin a 1:1 mixture of streptomycin and dihydrostreptomycin have been reported by Poutsiaka and co-workers[20]. Studies with experimental animals showed that the toxicity of these 2 drugs was not enhanced when administered together. Preliminary clinical studies on a small number of patients[11] showed that a mixture of 50% streptomycin and 50% dihydrostreptomycin produced no neurotoxic manifestations when administered in a dose of 1 gm. daily for 120 days. In a comparable control group either drug administered alone in the same amount produced neurotoxic manifestations in about 15% to 18% of patients treated.

Three other papers presented at the Twelfth Veterans Administration Conference on the Chemotherapy of Tuberculosis should be mentioned briefly. One by Hobby[12] summarizes a 4-year evaluation and present status of viomycin. In view of the urgent need of a well controlled study on the effects of chemotherapy with and without accompanying bed rest the discussion by D'Esopo[7] of a projected controlled systematic study of this problem is of great interest. The third paper concerns a review of 545 cases of genito-urinary tuberculosis treated on varying regimens and combinations of chemotherapeutic agents[14]. One year of combined therapy, together with nephrectomy or partial nephrectomy when indicated by extensive irreversible destructive lesions, brought about a figure of 85% bacteriological conversions of urine.

Several important experimental and laboratory studies on isoniazid have appeared within the past 6 months. Mackaness and Smith[16] have shown that in *in vitro* studies streptomycin and isoniazid possess comparable bactericidal activities in low concentrations, but that the effect of terramycin is almost entirely bacteriostatic. The combined use of isoniazid and streptomycin results in an acceleration of the death rate of both intracellular and extracellular bacilli. Terramycin, however, when used with isoniazid abolishes the bactericidal effect of the latter. Isoniazid is probably more effective in eliminating the intracellular source of streptomycin-resistant bacilli than PAS which is almost wholly inactive against intracellular bacilli. Other findings indicate that isoniazid is probably active only against actively multiplying bacilli. In contrast with the concept of a bactericidal action of isoniazid is the conclusion reached by Barclay and coworkers[2] employing radioactive isoniazid, that the initial action of the drug is bacteriostatic rather than bactericidal and may result by interference with the formation of an essential metabolite. Other studies on the action of isoniazid[4], and a series of its derivatives indicate that the introduction of a substitute for the pyridine ring or its reduction results in a loss of antituberculous activity. Further *in vivo* and *in vitro* studies on the combination of isoniazid and streptomycin [8,13] show that the synergistic effect of the 2 drugs occurs only in effective dosages and not when subeffective amounts are used, that the combination delays but does not entirely prevent the emergence of resistance to the other and that under certain conditions cross resistance may occur. It was again noted, however, that clinical improvement may continue in the face of some degree of resistance.

One extremely interesting and pertinent observation is that the presence of the ferric ion at an alkaline pH in the Dubos medium will inactivate isoniazid[21]. This is an important factor in the validity of resistance studies.

A very interesting clinical study on radioactive isoniazid[3] showed that after intramuscular injection, the highest concentrations of drug were present in lung and skin and that the drug diffused freely into dense caseous lesions in both lung and lymph nodes, high concentrations being present 3 to 5 hours after injection.

Further clinical information concerning the use of isoniazid is accumulating. Good results have been reported in its use in tuberculous sinuses and fistulas[5,18]. Studies in the treatment of miliary and meningeal tuberculosis[6,9,10] showed a definite favorable result in short-term studies as indicated by a more rapid return of the cerebrospinal fluid glucose levels to normal and a higher percentage of survivals. Strong arguments were presented by the Fitzsimons Hospital group against the need and advisability of intrathecal streptomycin.

Two significant reports on the combined use of streptomycin and isoniazid have appeared. Fitts and coworkers[19] report on a series of patients treated for 8 months on a regimen of 150 or 300 mg. of isoniazid daily combined with 2 gm. of streptomycin every third day compared with a group of patients receiving streptomycin and PAS. Preliminary evaluation on the basis of symptomatic response, weight gain, roentgenographic clearing and cavity closure favored the first group. Cavitation persisted in 54% of the patients on streptomycin and PAS and in

37% of the group receiving streptomycin and isoniazid. Culture negativity was present in 86 to 94% of the patients on either regimen 4 or more months. Although the high incidence of converted sputum made resistance studies difficult, there appeared to be a trend toward more frequent and rapid development of resistance on the streptomycin-isoniazid regimen than with streptomycin and PAS. No therapeutic difference was noted between 150 mg. and 300 mg. of isoniazid.

The United States Public Health Service study mentioned above has now been carried to the fortieth week[17]. During this period, 13 patients died of tuberculosis, 5 on the streptomycin-PAS regimen and 4 in both the isoniazid and streptomycin-isoniazid groups. Sputum cultures were persistently positive in approximately 20% of the streptomycin-isoniazid group and in approximately 30% of the patients in the other 2 groups. Roentgen-ray improvement occurred in 78% of the streptomycin-isoniazid patients, 71% of the streptomycin-PAS group and in 70% of the isoniazid patients. Five per cent of the first group and 7% of the 2 other groups showed roentgenographic deterioration. There was no significant difference in the bacteriological relapse rate.

The optimum choice of drugs in the treatment of tuberculosis is yet to be determined. The Committee on Therapy of the American Trudeau Society[1] still recommends the use of streptomycin-PAS as the chemotherapeutic regimen of choice in most patients with tuberculosis with streptomycin sensitive organisms. Tucker[23] has reported most promising results in the use of isoniazid and PAS for the treatment of streptomycin resistant cases. During the past 6 months no new information has accumulated which would necessitate revising the conclusions reached in the main portion of this paper. As stressed before, however, these conclusions are purely tentative and within another 6 months may need considerable modification.

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RADIOLOGY

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PROTECTION FROM ROENTGEN RAYS

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FROM the time of their discovery in 1895, Roentgen rays have been utilized at a rapidly accelerated rate in the diagnosis of many diseases. Indeed, the application of Roentgen radiation has become so extensive that many health physicists have become concerned lest the benefits of Roentgen diagnostic procedures be largely counterbalanced by the hazards which they carry. In view of this, it may be wise for us to review the dangers of exposure to Roentgen radiation and to indicate the measures by which these dangers may be minimized. Such a review is perhaps particularly desirable at this time because of the increasing number of physicians, using Roentgen radiation in their daily practice, who have not had specialized training in the field of radiology.

Early radiological workers did not anticipate the dangers of excessive radiation exposure, and few precautions were taken to protect either themselves or their patients. Not infrequently, radiologists placed their unprotected hands directly in the Roentgen beam, so that they could ascertain that their equipment was performing satisfactorily; if the hand could be seen on the fluoroscopic screen, the machine was known to be in good operating condition. Since such testing often took place several times a day over a period of many years, it is not surprising in view of what we know today that many of the early radiologists developed serious damage to their hands. Indeed, many pioneers lost one or more fingers from carcinomatous changes induced by excessive exposure to radiation[24].

The damage suffered by the early radiologists did not manifest itself immediately, but instead became apparent only after a period of several years. As a result, in a decade or two after the discovery of the Roentgen ray, the incidence of radiation-induced changes in the hands of radiologists increased at a rapid rate. It was at this time that the dangers of excessive radiation exposure were recognized and efforts to provide adequate protection from them were undertaken.

The Roentgen changes induced in biological tissues are manifold[2,4,7,12,21].

In diagnostic radiology, however, four anatomical systems are likely to suffer most seriously from excessive radiation exposure: (a) the cutaneous tissues; (b) the hemopoietic system; (c) the reproductive system; and (d) the osseous system (in children).

The cutaneous system is likely to suffer because the radiation used in diagnostic radiology is attenuated rather rapidly as it passes through the anatomical structures under examination. Hence, the intensity of radiation is greatest at the skin surface where the radiation enters the body close to the Roentgen tube.

The hemopoietic system[9] is of concern because the cellular elements of this system are among the most sensitive of any tissue in the body to the destructive action of Roentgen radiation. Quantities of radiation which have little effect upon such tissues as the nervous system, have a markedly destructive action upon the hemopoietic system.

The effects of excessive radiation exposure to the reproductive system[19,20] require consideration for two reasons. Like the hemopoietic system, its cellular elements are quite sensitive to ionizing radiation, and may be destroyed by relatively small quantities of it. Sterilization can occur, therefore, if the quantity of radiation received by the reproductive organs is sufficiently great. In addition, relatively small quantities of radiation have been observed to produce chromosome aberrations which lead to mutations in the succeeding generations of the individual who has been excessively irradiated.

Osseous tissues, in general, are relatively insensitive to Roentgen radiation. However, the growing portions of the bones of infants and children may be injured by even small quantities of radiation. The cellular elements of the metaphyseal plates appear to be easily impaired or destroyed by ionizing radiation and hence should be irradiated as little as possible in diagnostic Roentgen procedures.

It must be emphasized that the cutaneous, hemopoietic, reproductive and osseous systems are not the only tissues which suffer from excessive radiation exposure. However, because of the peculiar physical characteristics of the radiation used in diagnostic radiology and because of the particular sensitivity of the hemopoietic and reproductive cells, these are the tissues for which special care must be exercised in the protection of patient and physician.

a. SKIN. The changes which occur in the skin[5,12,21,22] are always localized in nature; the quantity of radiation necessary to produce even a temporary erythema, if applied generally to the entire body, would produce, in a large percentage of individuals, death from depression of the bone marrow. The changes which occur in the skin, therefore, are usually the result of a single large exposure to a localized area, such as the skin of the back in a gastrointestinal examination, or of multiple small exposures to a localized region, as in the skin of the hands of the early radiological workers[25].

The changes which occur in the skin may be immediate or may be delayed for several years. The immediate changes consist of a typical radiation erythema, which occurs from a few days to a few weeks after the diagnostic procedure has been conducted, depending on the size of the Roentgen dose which has been administered. The minimum quantity of radiation required to produce an erythema of the skin when radiation of diagnostic quality is employed is of the order of 300 roentgens[10].

In fluoroscopic practice, instruments which include proper filtration and which are operated at proper voltage

and tube current deliver approximately 6 roentgens per minute to the skin of the patient under examination. However, Sonnenblick *et al.*[26] in a recent survey, found many fluoroscopes in frequent use in physicians' offices which have outputs of 90 to 100 roentgens per minute. It is quite evident from this that although a fluoroscope which has a low roentgen output is not likely to be a hazard as far as immediate cutaneous reaction is concerned, fluoroscopes with outputs as high as 100 roentgens per minute constitute a very serious hazard. In later paragraphs, we shall review the requirements for safe fluoroscopic operations which, if exposures are confined to three to five minutes, will avoid the hazards of cutaneous reaction.

When the skin is given a single exposure of 300 roentgens and an erythema subsequently appears, the changes will be temporary in nature, and usually the erythema will completely disappear in a period of a few weeks. No delayed reaction may be expected under these circumstances. However, if the patient is fluoroscoped many times over a period of years so that the total quantity of radiation delivered to a particular area amounts, perhaps, to several thousand roentgens, very serious manifestations will appear. The early radiologist, for example, who exposed his hands to only two or three roentgens per day, experienced no erythema or other immediate reaction. However, in a period of 5 to 10 years after a total of several thousand roentgens had been delivered, catastrophic changes to which we have referred began to appear.

Hyperkeratosis and telangiectasis may be expected to develop first. If the exposure continues, the cutaneous tissues break down and squamous carcinoma develops at intervals over the skin surface. It is difficult to say how much radiation is required to produce these long-term changes. Experience from radiation therapy, however, indicates that the total quantity probably must exceed 5,000 roentgens[15,21]. There is, however, considerable individual variation, and doubtless there are on record individuals who developed long-term changes of the skin with smaller quantities of radiant energy. It is evident that a patient may be examined many times with a fluoroscope operating at 6 roentgens per minute without the possibility of skin damage occurring. On the other hand, it is equally apparent that improperly controlled fluoroscopes of the type found by Sonnenblick *et al.*[26] may induce serious damage after a relatively few examinations.

In this discussion of cutaneous damage from excessive radiation exposure, we have referred only to the damage which occurs to the patient. The reason for this is that it is the patient who bears the full impact of the direct radiation generated by the Roentgen tube. The fluoroscopist seldom introduces his hands or other structures into the direct Roentgen beam, and then only in that portion of the beam as it emerges from the patient. Even so, the physician should be extremely careful of the placement of his hands within the direct Roentgen beam, particularly if he does a great deal of fluoroscopy. If 3 roentgens per day are received by a fluoroscopist's hands, in ten years the quantity of radiation to which the hands have been exposed will exceed 10,000 roentgens. The possibility of irreversible changes occurring within the hands within a short time thereafter will be very real. Since even a safe fluoroscope will deliver a dose of 6 roentgens per minute in the unattenuated state, it is quite evident that fluoroscopy should never be undertaken without the wearing of leaded gloves by which the radiation dosage is sharply attenuated. Fortunately, cur-

rently available gloves reduce the radiation dosage by a factor of some 150 times.

b. HEMOPOIETIC SYSTEM. The effect of radiation on the hemopoietic system, like that on the cutaneous system, may be either immediate or delayed[9,12,13]. The immediate reaction is one of leukopenia and depression of the bone marrow. If these changes occur, and if the radiation is continued or prolonged over a period of time, the depression of the bone marrow may become permanent. Also, experiments in mice indicate that when radiation is given to major portions of the hemopoietic system in sufficient quantities, leukemia will develop. There have been some studies which appear to indicate that leukemia is more prevalent among radiologists and other physicians who use Roentgen radiation than in the general population. Although this relationship is difficult to prove from the statistical evidence at hand, it seems fairly clear that excessive radiation of long-standing duration can produce malignant changes in the blood-forming tissues.

Damage to the hemopoietic system is much more likely to occur in physicians who use fluoroscopy than in the patients who are fluoroscoped. The reason for this is quite simple[28]. Patients undergoing fluoroscopy receive radiation which is concentrated in relatively small regions of their bodies by the limiting shutters in front of the Roentgen tube. The quantity of radiation received by the hemopoietic system, distributed widely throughout the body, is, therefore, not likely to be great. On the other hand, the fluoroscopist is exposed generally over his entire body by radiation which is scattered in all directions by the patients under examination. Although the intensity of this radiation is quite small, the fluoroscopist who has a busy practice is likely to receive considerable quantities of radiation over a period of time. Indeed, the summation of the radiation from many patients distributed widely over the physician's body is likely to cause serious trouble to the hemopoietic system unless adequate protective measures are followed.

It should perhaps be emphasized to the reader who is not familiar with the distribution of the radiation about a fluoroscope that the radiation to which the fluoroscopist is subjected is not the radiation emanating directly from the Roentgen tube, but instead is radiation scattered by the patient under examination. This radiation is dispersed in all directions, and hence is widely distributed. Compared to the dosage of the direct Roentgen beam as it falls on the patient, the intensity of this scattered radiation is not great. If the size of the irradiated field is small (8 x 10 inches), the dosage occurring to the side of the fluoroscope need not exceed 2 roentgens per hour and lower dosage rates may be maintained at other positions. However, it is evident that a few hours of fluoroscopy each week will soon deliver sizeable Roentgen doses to the physician if protective devices are not employed. Furthermore, the quantity of the scattered radiation rises very rapidly when the size of the irradiated field is increased; that is, the quantity of scattered radiation increases markedly as the shutters of the fluoroscope are opened to include larger and larger portions of the body for examination[28].

It appears that an exposure of more than a few roentgens per week is likely to cause depression of the bone marrow of an individual if the radiation is delivered over the entire body[9]. Since the radiation received by the fluoroscopist is directed widely over his body and since the dosage from even a properly operating fluoroscope may amount to several roentgens per hour

of fluoroscopy, it is clear that hemopoietic damage may readily occur if the radiation dosage is not reduced by suitable protective measures. Such measures include the wearing of leaded aprons and gloves. Also, since scattered radiation may be significantly reduced by the maintenance of the fluoroscope's shutters at a small aperture, the fluoroscopist should confine his field of examination to the smallest possible size. Finally, the factors which tend to reduce radiation exposure in the patient (proper filtration and proper operating kilovoltage and milliamperage) also reduce the quantity of scattered radiation to which the fluoroscopist is exposed; the factors which lead to low radiation exposure of the patient are, therefore, important to the fluoroscopist as well.

Because of the relative sensitivity of the hemopoietic system to damage from exposure to excessive radiation, the maximum permissible exposure of the total body of an individual during any given week should not exceed 0.3 roentgens (300 milliroentgens)[23]. This value has been derived only after considerable discussion by many authoritative groups[27]. Unfortunately, the figure is not based upon direct experimental evidence, since such evidence cannot be practicably determined for human beings. However, the figure does represent the thinking of a large number of people who have had a great deal of experience within the field of radiation.

c. REPRODUCTIVE SYSTEM. There has been considerable speculation in the past two decades concerning the effect which Roentgen radiation may have on future generations of man through mutations induced by either acute or chronic irradiation. Muller[18] has shown that the natural rate of appearance of new mutations in the fruitfly could be increased with irradiation with Roentgen-rays. Although the quantity of radiation required to produce such changes in man is not known, it apparently amounts to several hundred roentgens, since Lorenz and Heston[14] have found that mice bred from five to six generations while continuously exposed 24 hours a day to 1.1 roentgen and 0.11 roentgen of gamma radiation showed no damage to chromosomes as evidenced by normal litter size and apparently normal life span. Also, Deringer and his colleagues[3] exposed mice chronically to accumulated Roentgen doses of 770 roentgens for females and 1100 roentgens for males; no evidence of the production of visible genetic changes was obtained in the immediate offspring of the mice so irradiated. Geneticists are quick to point out, however, that since Roentgen-induced mutations are usually recessive, they may not be evident for several generations.

The changes which are induced in the chromosomes of germ cells by Roentgen radiation include chromosome breakage and translocation. These changes apparently are the result of the direct action of the ionization within the nucleus following the absorption of the radiant energy[11].

When the genetic significance of Roentgen radiation is evaluated, it must be remembered that all organisms exhibit spontaneous gene mutation rates which are quite unrelated to exposure to Roentgen rays. These spontaneous mutations are identical in every way to mutations induced by radiation. Therefore, the genetic effect of radiation is simply to increase the number of mutations. In man, spontaneous mutations which are due to causes other than radiation occur at a rate of about one in 100,000 genes per generation[6]. Interestingly, this rate is not much different for other organisms, and hence it is believed that in long-lived organisms such as man, the gene material is somewhat more stable per

unit of time than in short-lived organisms.

Although reliable data have been collected concerning the effect of Roentgen radiation on the mutation rates of a large number of organisms, such studies have not been possible in man because of obvious experimental difficulties. It has, therefore, been necessary to resort to extrapolation of animal data in order to arrive at an estimate of the increase in mutation rate that will be produced by radiation in the human. Evans[6], in a comprehensive study of the subject, presents information which makes it appear that no detectable increase in the mutation rate of man is likely to occur, even after many generations, if a small fraction of the population receives daily radiation dosages of 0.1 roentgen throughout life. Indeed, in the population as a whole, it appears that the mutation rate may be expected only to double the spontaneous mutation rate if 140 roentgens are delivered to everyone during the fecund period. Many geneticists feel that no significant eugenic harm would be done if not more than double the spontaneous mutation rate were to occur. There is, however, a recent tendency of some geneticists to become somewhat more conservative because, perhaps, of the fact that all of the calculations that have been made for man constitute extrapolated values from data on animals. Hence, the belief is growing that the total accumulated dose to the reproductive organs of an individual during his reproductive life should not exceed 50 roentgens[8].

With the application of suitable protective measures, both to the patient and to the physician who uses Roentgen radiation in his practice, a dosage to the gonads of less than 50 roentgens should not be difficult to maintain. Fortunately, the reproductive organs of young individuals are not located in anatomical regions that are likely to be the site of pathological change. Hence, the reproductive organs are seldom irradiated directly in diagnostic procedures of persons less than 40 years of age.

Of course, irradiation of other structures such as the chest will be accompanied by some irradiation of the reproductive organs through scattering. The quantity of this scattering, however, is relatively small, and may be expected to amount to less than 1% at a distance of one foot from the site of the primary irradiation. The quantity of scattered radiation will fall considerably below this value, if the size of the irradiated area is small.

As has been pointed out previously, the Roentgen dosage of the direct radiation falling upon a patient during fluoroscopy, when adequate protective techniques are employed, need not exceed approximately 6 roentgens per minute. Also, in the case of radiography, the radiation exposure delivered during various diagnostic procedures ranges from 0.05 roentgens for conventional roentgenograms of the chest to 5 roentgens for films of the lateral lumbar spine[17]. Photofluorograms of the chest impose an exposure of approximately 1 roentgen. It is quite evident from these values that considerable fluoroscopy and roentgenography of structures *remote* from the reproductive organs can be carried out on patients without creating hereditary difficulties in future generations. It must be emphasized, however, that although satisfactorily controlled fluoroscopes and radiographic machines appear to be quite safe, even minor irregularities in the design and operation of such equipment may lead to serious difficulty. It is, therefore, extremely desirable that fluoroscopic and radiographic equipment be operated with as many safeguards as possible and with the application of just

as little radiation to the patient as is possible.

d. OSSEOUS SYSTEM. Osseous tissues are relatively insensitive to Roentgen radiation. Hence, it is only in children where the growing ends of the bones may be damaged that concern need be expressed for excessive radiation exposure. Barr and his colleagues[1] have found that a few hundred roentgens delivered to the epiphyses of albino rats cause considerable retardation of bone growth. Single doses were somewhat more effective than divided doses.

It is clear that in infants and children, fluoroscopy and radiography should be used sparingly and then only fluoroscopes of low Roentgen output should be employed. Although recovery of osseous tissue occurs after irradiation, repeated fluoroscopies of several minutes in children will soon bring the accumulated dose to hazardous levels. Although human data are not available, it is apparent from the work of Barr and his group that a cumulative radiation dosage of more than 100 roentgens should be avoided in children if at all possible.

From the evidence cited in the foregoing paragraphs, it is amply clear that the exposure of one's patients and of oneself to Roentgen radiation should not be taken lightly. It should also be clear, however, that the danger of injury is not great if caution and common sense are employed in the performance of diagnostic Roentgen procedures.

As a basic rule, the physician should remember that Roentgen equipment should always be operated under conditions such that the lowest possible quantity of radiation consistent with adequate anatomical visualization is delivered to the patient. For fluoroscopic equipment this requires the meticulous observation of the following standards:

(a) The inclusion of 3 mm. of aluminum filtration in the incident Roentgen beam;
(b) The restriction of the size of the field of irradiation to less than 8 by 10 inches;
(c) The maintenance of the tube-to-patient distance at a value of not less than 18 inches;
(d) The restriction of the exposure time of any given patient to less than 5 minutes; and
(e) The restriction of the Roentgen tube current to 5 ma or less.

With the observation of these standards, approximately 6 roentgens per minute will be delivered to the skin of patients for Roentgen tube potentials of 85 kvp or less.

In addition to the protective measures just listed, leaded apron and gloves must be worn by the physician if his own exposure is to be reduced to a minimum. Leaded aprons of the type generally available today have a lead equivalent of 0.4 mm. and attenuate 80 kilovolt radiation approximately 125 times. Leaded gloves are available in several equivalents; those having an equivalent of 0.5 mm. attenuate 80 kilovolt radiation approximately 150 times. With such aprons and gloves, several hours of fluoroscopy are permissible each week without great risk.

In regard to the filtration of the Roentgen beam, Morgan[16] has shown that the radiation exposure to the patient may be reduced by a factor of several times by the inclusion of 3 mm. of aluminum between the Roentgen tube and patient. Such filtration removes essentially all of the soft, useless components of the radiation and hence reduces the radiation exposure to the patient without noticeably reducing the brightness of the fluoroscopic screen.

The size of the field of irradiation has a profound effect upon the radia-

tion exposure of both the patient and the fluoroscopist[28]. The effect upon the patient is quite obvious. Many physicians frequently overlook the fact that large fields of examination are likely to increase the dosage to which they are exposed very markedly. The quantity of radiation scattered from the patient to the physician varies proportionately to the area of the irradiated field. Hence, a fluoroscope whose shutters are opened so that the field under examination is approximately 11 by 14 inches will result in almost five times the exposure to the fluoroscopist as that of a fluoroscope whose shutters are restricted to a 5 by 7 inch field. Since the hazards of large-field fluoroscopy are not likely to be appreciated by many physicians until serious damage to themselves occurs, it is the opinion of many workers[16] that fluoroscopic equipment should be manufactured so that field sizes in excess of 8 by 10 inches cannot be obtained.

There has been a practice among some physicians to increase the milliamperage of the fluoroscopic equipment to values considerably in excess of 5 milliamperes. This is usually done to increase the brightness of the fluoroscopic screen and to reduce the need for lengthy periods of dark adaptation[26]. Such a practice, however, cannot be too strongly condemned. Since the radiation dosage to the patient varies proportionately to the milliamperage, the possibility of severe radiation reaction of the skin, hemopoietic and reproductive tissues is likely to occur sooner or later to some patient whose susceptibility to radiation is greater than usual. For similar reasons, the use of long exposure times during fluoroscopy is also to be avoided. It is, therefore, strongly recommended that fluoroscopic equipment always include an interval timer which will limit the exposure to any given patient to a value of 5 minutes or less.

In these discussions, the emphasis has been on the hazards of fluoroscopy. Serious dangers also may occur in radiography by repeated examination of a particular structure. Radiation dosage to the patient may be minimized, however, by the observance of many of the standards recommended for fluoroscopy. The use of 3 mm. of aluminum filtration in the Roentgen beam, the adoption of a long tube-film distance (36 inches or more) and the restriction of the irradiated field to the smallest possible size will serve to reduce the exposure to which the patient is subjected.

Protection of professional and technical personnel in radiographic installations requires the installation of barriers between equipment and personnel locations sufficient to reduce the radiation dosage levels to less than 0.3 roentgen per week. Convenient data, which require no tedious mathematical calculations, are now available by which barrier requirements for a wide range of diagnostic installations may be easily determined[17]. If these data are followed in the design of Roentgen installations and if the easily applied fluoroscopic recommendations made in preceding paragraphs are employed, the problems of radiation protection in diagnostic radiology will be greatly minimized.

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BOOK REVIEWS AND NOTICES

RECENT ADVANCES IN CLINICAL PATHOLOGY. Edited by S. C. DYKE, D.M. (OXON), F.R.C.P., (London), Pathologist, The Royal Hospital, Wolverhampton. 2nd ed. Pp. 575; 63 ills. New York: The Blakiston Co., 1951. Price, $6.00.

THE second edition of this work has kept pace with the rapid progress in clinical pathology. The major sections encompass most of the important advances in Bacteriology, Biochemistry, Hematology, and Histology. In addition, there is a special section devoted to Laboratory Design and Equipment. The editor and the 32 contributors are all highly qualified workers in their respective fields. Together they have produced an authoritative manual which will be valuable to clinicians and clinical pathologists alike. C. Z.

BCG VACCINATION, Studies by the WHO Tuberculosis Research Office, Copenhagen. By LYDIA B. EDWARDS, M.D., Chief of Field Studies and CARROLL E. PALMER, M.D., Ph.D., Director, with the assistance of KNUT MAGNUS, cand. act., Assistant Statistician. Pp. 307; 53 ills. Geneva: World Health Organization, 1953. Price, $3.00.

THIS monograph, the latest in the World Health Organization series, sets forth the results of studies on BCG vaccination conducted under the direction of the World Health Organization Tuberculosis Research Office. The investigations were undertaken as part of the International Tuberculosis Campaign sponsored by various international health agencies. The studies were designed to elucidate various problems that arose in the course of large-scale BCG vaccination campaigns carried out in many war-disrupted countries. More than 40,000 school children in four countries constituted the study population on which 27 separate studies were conducted. Included are studies of tuberculin testing, both preparatory to and after BCG vaccination, techniques of vaccination and the preparation and handling of the vaccine.

There are interesting findings in every chapter of the report. For the general reader, perhaps the most interesting will be those having to do with tuberculin sensitivity. The authors stress in their general summary that tuberculin sensitivity is quantitative and cannot be thought of in qualitative terms, as something the body does or does not possesss. By quantitative measurement qualitative differences may be revealed, however. Strong evidence is presented to support the view that there are at least two different kinds of accidentally acquired sensitivity to tuberculin. One kind, found everywhere, is manifested by a strong reaction to a weak dose. This high-grade sensitivity is undoubtedly caused by infection with virulent tubercle bacilli. The other kind, not found everywhere, is reflected in smaller reactions to the same weak dose, and is generally designated as "nonspecific." This type of response is apparently unrelated to tuberculous infection, though the cause is still unknown.

In addition to the text and tables in the main body of the report there is an appendix giving complete quantitative data for all of the tests and examinations carried out. The monograph is a source book for anyone interested in BCG.

In this reviewer's opinion the monograph could be used by anyone as a guide in designing, performing and reporting experiments on human beings. D. O.

PHANTOME UND DOPPELGÄNGER. By PROF. DR. MAX MIKOREY, Munich. Pp. 72. Munich: J. F. Lehmanns Verlag, 1953. Price, DM 6.00.

A noteworthy presentation of the subject of phantom limbs and other portions of the human body, in which the author leads step by step from the sphere of anecdotes and curiosities to the threshold of the highest problems of humanity. Really it forms the groundwork for a "psychological anthropology." Man is a phantom-forming type of life (and apparently the only one). Starting from the demonstration that phantom limbs arise from, as it were, the frustrated or compensated-for regenerative capacity of certain lower forms, such as kinds of worms, of forming new individuals when divided, or of the salamander of regenerating amputated limbs; man has the capacity, in cases of completely amputated limbs, high up, of feeling that such limbs are still attached to the body; in fact he may dispense with prosthetic appliances, feeling that they are in the way. The author regards this capacity as "metaneurologic", and man has the privilege of possessing it. In

certain cases it may serve as of psychotherapeutic value. It may be combatted or (in cases) aided by the process of autotomy or of self-amputation as manifested in crabs, for instance, of getting rid of an injured claw that subsequently regenerates. This in man and the higher animals is represented by the line of demarcation that follows severe injuries to limbs. In time, the distal parts of the phantom may become as if "telescoped" into the proximal parts. Here the phantom resembles the actual condition in cases of phocomelia.

There are cases in which the subjects of hemiplegia or of certain spinal cord injuries feel as if the defective side of the body were still intact and functioning. Such cases may be ascribed to the so-called "twin-reflex", in which the subject feels the regenerative power of the part that may have become a twin if the ovum whence the individual originated had divided longitudinally in the early stages of its existence. In some cases the imaginary "twin" may amount to a veritable "double". This may occur, for instance, in the epilepsies and in the exogenous and the endogenous psychoses; also in cases of severe mental conflict, as in the case of Goethe as recorded in his autobiography.

The author takes a philosophical view of these phenomena, citing philosophers and literary men, and believes that the occurrences are manifestations of the relative primitiveness of the human soma, as manifested, for instance, in the structure of the human hand. Because of it man has become the tool-using and tool-devising animal, and it lies at the root of his spiritual and religious aspirations. In fact the author might have said, "It leaves him only a little lower than the angels." M. M.

TEXTBOOK OF CLINICAL PATHOLOGY. Edited by SEWARD E. MILLER, M.D., Med. Dir., U.S.P.H.S., Chief Division of Occupational Health. 4th ed. Pp. 1060; 245 ills., 33 in color. Baltimore: Williams & Wilkins Co., 1952. Price, $9.00.

THE previous editions of this textbook were edited by the late Dr. Roy R. Kracke and Dr. Francis P. Parker. Under the editorship of Dr. Miller, the fourth edition has been extensively revised. Emphasis is placed on basic scientific facts, interpretation, and evaluation of laboratory diagnostic procedures. Detailed descriptions of technical methods which are carried out by skilled laboratory technicians are omitted, while those usually performed by medical students, interns and other medical personnel are portrayed step by step.

The sections are generally well written. The newer terminology in hematology has been adopted and is used throughout. The authors are to be congratulated for discouraging the practice of routine red blood cell counts. The chapter dealing with the diagnosis of virus and rickettsial diseases is outstanding in its clear presentation of difficult subject matter.

As a textbook of clinical pathology, the present edition meets most of the needs of medical students, interns, and practising physicians. C. Z.

PROGRESS IN CLINICAL MEDICINE. By RAYMOND DALEY, M.A., M.D. (Camb.), and HENRY G. MILLER, M.D. (Durh.). 2nd ed. Pp. 426; 43 ills. London: J. & A. Churchill, Ltd., 1952. (U. S. Agent, John de Graff, Inc., New York). Price, $6.50.

THE second edition of this work attempts to summarize the medical advances which were made during the three years which elapsed after the first report of this series. Thirteen contributors deal with an equal number of diverse fields, ranging in scope from industrial to psychosomatic medicine. While there is much of interest in each section, the volume is not likely to find extensive use in this country since much more comprehensive reviews are available here on a yearly basis. C. Z.

ANALGESIA AND ANESTHESIA IN OBSTETRICS. By J. P. GREENHILL, M.D., Professor of Gynecology, Cook County Graduate School of Medicine. A Monograph in American Lectures in Gynecology and Obstetrics. Pp. 83; 11 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $2.75.

DR. GREENHILL, in this monograph, briefly discusses agents used for obstetrical analgesia, inhalation anesthetic agents, intravenous anesthesia, and regional anesthesia. The use of the Grantly Dick Reed's Technique and hypnosis are also mentioned.

The section on hypodermic, oral and rectal agents is very well done, as well as his sections on regional anesthesia, with the exception of spinal anesthesia.

Dr. Greenhill's presentation of the section on inhalation agents is too brief and contains very little real information. The space could have served a more useful purpose if the author had described the technique of admin-

istering one or two inhalation agents as required by the patient and obstetrician depending upon the course of labor and type of delivery.

Spinal anesthesia, if administered properly is a very satisfactory type of anesthesia. It has proven to be one of the best types of anesthesia for cesarean sections if used by trained physicians. I agree with Dr. Greenhill that spinal anesthesia is most dangerous only if used by inexperienced physicians.

L. K.

AN ATLAS OF THE COMMONER SKIN DISEASES, With 147 Plates Produced By Direct Colour Photography From the Living Subject. By HENRY C. G. SEMON, M.A., D.M. OXON., F.R.C.P. LONDON, Consulting Physician for Diseases of the Skin and Former Lecturer to Postgraduates, Royal Northern Hospital. 4th ed. Pp. 371; 147 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $13.50.

THE fourth edition of this book, which first appeared in 1934, is a collection of 147 plates in natural color of the dermatoses most frequently seen in the routine outpatient practice. There are also abbreviated descriptions, tables of differential diagnosis, and pertinent treatment suggestions. In addition to the commoner processes, there is material on some of the diseases more rarely encountered. An adequate index completes the volume. Since most of the pictures allow objective diagnosis by an experienced dermatologist, it is understandable why this work has gone through four editions. But all is not perfect, inasmuch as some of the color plates could be greatly improved (for example, Plate XXII, page 67). Colloquial expressions (for example, mollusca) and the lack of illustrations of Negro patients are to be expected in an English book. The alphabetical presentation of the subjects considered causes a lack of continuity. The therapy of syphilis is a little out-of-date. In spite of these shortcomings, the Atlas may be used as a refresher on everyday clinical dermatology for the interested reader. H. B.

PRINCIPLES AND TECHNIQUE OF EXODONTIA. By FRANK WENDELL ROUNDS, A.B., D.D.S., Sc.D. (Hon.), Late Dental Surgeon to Brooks Hospital, Courtesy Staff, Phillips House, Massachusetts General Hospital, and CHARLES ELDER ROUNDS, A.B., D.D.S., D. M. D., Assistant Dental Surgeon, Massachusetts General Hospital, Visiting Instructor in Oral Surgery, Tufts Dental School. Pp. 407; 365 ills. St. Louis: C. V. Mosby Co., 1953. Price, $10.00.

THE book is of convenient size for ready reference by both dental students and general practitioners of dentistry. It is well illustrated and covers, in detail, the various problems which the exodontist, either as a specialist or as a general practitioner, usually encounters.

Much of the technique advised in tooth extraction and the instrumentarium recommended follows closely the monumental work on "Exodontia", advocated by the late George B. Winter (Exodontia: Extraction of Teeth, George B. Winter, St. Louis, American Book Co., 1913; Principles of Exodontia as Applied to the Impacted Mandibular Third Molar, George B. Winter, St. Louis, American Book Co., 1926). This is to be expected as Dr. Frank Rounds was both a student and close friend of Doctor Winter.

There are 28 chapters in the book, each containing definite principles to be followed in the successful, non-traumatizing technique of tooth extraction. Considerable credit should be given the authors in presenting a definite refinement of tooth extraction technique which can easily be followed and put into practice. The book is highly recommended for use as a reference and guide to those interested in this branch of dentistry.

J. C.

THE PHYSICIAN IN ATOMIC DEFENSE. ATOMIC PRINCIPLES, BIOLOGIC REACTION AND ORGANIZATION FOR MEDICAL DEFENSE. By THAD P. SEARS, M.D., F.A.C.P., University of Colorado School of Medicine. Pp. 308; 53 figs. Chicago: Year Book Publishers, Inc., 1953. Price, $6.00.

THIS book was written with a deep conviction that communities should be prepared for atomic warfare and a determination to arouse civilians and the medical profession from their unrealistic complacency. Easy to read and logical in arrangement, it covers the essentials of the structure and physics of the atom in relation to radioactivity and its applications, the use of isotopes, and the mechanism and hazards of the atomic bomb. Also the clinical, biologic, pathologic and therapeutic aspects of atomic warfare with the organization and methods for medical and civil departments for atomic defense. Furthermore, since the atomic age is here with an increasing use of atomic energy for industrial purposes, the symptoms, pathology, prevention, and treatment of radioactive effects are concisely presented because of their imme-

diate interest to the medical profession with particular reference to industrial physicians and radiologists. J. K.

THE 1952 YEAR BOOK OF NEUROLOGY, PSYCHIATRY AND NEUROSURGERY. Neurology, edited BY ROLAND P. MACKAY, M.D., Professor of Neurology, University of Illinois; Psychiatry, edited by NOLAN D. C. LEWIS, M.D., Professor of Psychiatry, Columbia University; Neurosurgery, edited by PERCIVAL BAILEY, M.D., Professor of Neurology and Neurological Surgery, University of Illinois. Pp. 603; 121 ills. Chicago: Year Book Publishers, 1953. Price, $6.00.

THIS year book maintains the high standards of previous editions. It is divided into three sections as the title indicates. The type is easy to read and the illustrations are excellent.

The editors are eminently qualified to decide which contributions merit a place in their sections but some excellent articles must be omitted in a book of this type because of the space factor.

Perhaps this objection could be overcome by a thorough bibliography at the end of each section and thus make the book a more valuable source reference.

This annual year book needs no praise. It has proven to be valuable throughout the years and is regularly read by those interested in its specialities. It should prove particularly helpful and stimulating to residents in these specialties and to the general practitioner. M. S.

PROTEIN METABOLISM, HORMONES AND GROWTH. Edited by WILLIAM H. COLE. Pp. 80; 30 ills. New Brunswick: Rutgers University Press, 1952. Price, $1.50.

THIS small volume contains six informal lectures presented at the Eighth Annual Conference on Protein Metabolism held at Rutgers University in 1952. The subjects covered include: 1) Effect of protein and amino acids of the diet on the endocrine system (by L. T. Samuels); 2) Relationships between the thyroid and protein metabolism (by J. H. Leathem); 3) Some aspects of the protein anabolic action of the androgens (by C. D. Kochakian); 4) Relationship between the adrenal cortex and protein metabolism (by F. L. Engel); 5) Effects of growth hormone on metabolism of nitrogen (by J. A. Russell); and 6) Hormonal regulation of human growth (by L. W. Kinsell).

These presentations will be of interest especially to those actively engaged in the respective fields. C. Z.

THE INTERPERSONAL THEORY OF PSYCHIATRY. BY HARRY STACK SULLIVAN, M.D. Pp. 393. New York: W. W. Norton & Co., 1953. Price, $5.00.

THIS is a collection of hitherto unpublished lectures on concepts of psychiatry given by the recently deceased and highly respected Harry Stack Sullivan at the Washington School of Psychiatry. They follow chronologically through the various developmental stages of emotional growth describing, in the author's colorful language, his inferences of human emotional interaction between the child and those with whom he comes in contact. Chapters are devoted to serious mental disorders, to dreams and myths and to a "psychiatry of people." The author's vocabulary differs somewhat from the Freudian school but the evaluation of events of growth in the production of the eventual personality which emerges is essentially the same. It is a detailed presentation but readable and tied in with many observations on the effects of social values on personality formation.

O. E.

ORAL SURGERY. BY KURT H. THOMA, D.M.D., F.D.S.R.C.S., (Eng.), F.D.S.R.C.S., (Edin.), Professor of Oral Surgery, Emeritus, and Brackett Professor of Oral Pathology, Emeritus, Harvard University. 2nd ed. Two volumes. Pp. 1688; 1798 ills., including 121 in color. St. Louis: C. V. Mosby Co., 1952. Price, $30.00.

THE two volumes are completely revised from former texts dealing with oral surgery by Doctor Thoma.

The author has included a special chapter on, "Chemo-therapy and Antibiotic Therapy" and brings the reader up-to-date on the use of these agents in the changing concept of practice since their advent in the field of surgery.

Chapter 7, "The Treatment of Traumatic Diseases of the Jaws" covers in great detail the many injuries affecting the maxillary bones. The author leans strongly to wiring fractures of the neck of the condyle. This procedure, while valuable and certainly indicated in many cases of condylar fractures, is not generally accepted by all oral surgeons. Alternate methods of treatment, however, are discussed and evaluated.

Chapter 6, dealing with, "The Treatment of Abnormalities of the Edentulous Mouth" is a valuable contribution to the oral surgeon and the prosthodontist, as is Chapter 10 covering, "The Diseases of the Mandibular Joint."

With the increased interest and responsibility of the dental profession in, "Neoplastic Lesions Affecting the Oral Cavity and Associated Structures," Chapters 15 and 16 convey much valuable information. The modern dentist, and the dental specialist in oral surgery, have a tremendous responsibility in the early recognition of precancerous lesions and of malignant growths in, and about, the mouth and jaws. The two chapters mentioned cover the subject in an excellent manner.

It is to be regretted that the treatment of cleft lip and cleft palate has been omitted from a two-volume text on "Oral Surgery." These deformities are within the field of oral surgery and might well have been covered; especially, the present day concept of what prosthodontists are accomplishing in the way of speech appliances. It seems, to this reviewer, that less cleft palate surgery will be done in the future if dentists interested in prosthesis will undertake the task of rehabilitating unfortunate individuals born with cleft palate.

The two volumes present the subject of oral surgery in a manner that is readily available as a reference. It is well-illustrated and the technical procedures adequately explained for guidance of dentists, oral surgeons, and general surgeons. J. C.

Blood Cells and Plasma Proteins: Their State in Nature. Edited by James L. Tullis. Pp. 436; 102 ills. New York: Academic Press, Inc., 1953. Price, $8.50.

This basic volume is an outgrowth of a series of seminars held at Harvard University by the Laboratory of Physical Chemistry Related to Medicine and Public Health. Twenty-nine outstanding investigators have contributed to this work which is divided into 7 major sections: 1) The formed and the fluid parts of human blood: their discovery, characterization, and separation by virture of their physical properties and chemical reactions. 2) The factors concerned with blood coagulation. 3) The components of human blood concerned with immunity. 4) Erythrocytes. 5) Leukocytes. 6) The enzymes of plasma. 7) The lipoproteins of blood and other tissues.

The fundamental nature and broad scope of the subjects covered make this a valuable reference volume for workers in many disciplines. C. Z.

Hypersplenism and Surgery of the Spleen. By William Dameshek, M.D., and C. Stuart Welch, M.D., Pp. 84; 105 ills. New York: Grune & Stratton, 1953. Price, $10.00.

This work graphically presents an up-to-date account of the spleen and disorders of hypersplenism. The anatomy and physiology of this organ are discussed as are the physiologic effects of splenectomy. Various hypersplenic syndromes, pre- and post-splenectomy, are illustrated with selected cases. Included are examples of Gaucher's disease, cirrhosis of the liver, tertiary syphilis, Hodgkin's disease, leukemia, Felty's syndrome, primary splenic neutropenia, primary splenic pancytopenia, acute hemolytic anemia, hereditary spherocytosis, acquired hemolytic anemia, and idiopathic thrombocytopenic purpura.

A comprehensive approach to the study of a patient with splenomegaly is outlined. Indications and contraindications for splenectomy are discussed, and there is included a discussion of the surgical aspects of this operation.

The authors are internationally recognized for their many contributions in the field of hematology. Their present work is both interesting and instructive and should prove valuable to physicians and medical students alike. C. Z.

Individual and Community Health. By William W. Stiles, M.D., M.P.H., Associate Professor of Public Health, University of California, Berkeley. Pp. 492; 134 ills. New York: Blakiston Co., 1953. Price, $6.00.

This excellent book was written primarily for teaching at the college level the principles of individual and community health. The reviewer hopes that such instruction will ultimately be given to all students in all colleges although, at the present time, this is still to be approached with a missionary spirit because general interest in these subjects continues to lag. As stated in the preamble to the constitution of the World Health Organization, "The extension to all peoples of the benefits of medical, psychological and related knowledge is essential to the fullest attainment of health. . . . Informed opinion and active co-operation on the part of the public are of the utmost importance in the improvement of the health of the people." Certainly

present knowledge on the protection and promotion of individual and community health, which is so clearly and concisely presented in this book, should be made a part of the education and equipment of all college students regardless of the professions or other activities for which they are preparing. J. K.

TEXTBOOK OF VIROLOGY. BY A. J. RHODES, M.D., F.R.C.P. (EDIN.) and C. E. VAN ROOYEN, M.D., M.R.C.P. (LOND.). 2nd ed. Pp. 561; 76 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $8.00.

THE authors have succeeded in preparing an up-to-date textbook covering the essential features of the virus and rickettsial diseases of man. The volume is particularly suitable for medical students and others interested in an introduction to these groups of infectious diseases. Advanced workers, however, will prefer the much more comprehensive treatise by the same authors (Virus Diseases of Man, 2nd Edition, Thomas Nelson and Sons, New York, 1948). C. Z.

PHARMACOLOGY AND TOXICOLOGY OF URANIUM COMPOUNDS. PARTS 3 AND 4. CHRONIC INHALATION AND OTHER STUDIES. Edited by CARL VOEGTLIN, Ph.D., and HAROLD C. HODGE, Ph.D. National Nuclear Energy Series VI-I, two volumes. Pp. 1350; illustrated. New York: McGraw-Hill Book Co., 1953. Price, $18.00.

THIS work bound in two volumes is a continuation of Parts 1 and 2 (published in 1949 and reviewed in **219**, 113, 1950) of the investigations of a number of scientists on the pharmacology and toxic properties of uranium compounds. Part 3 (Chapters 18-22) is concerned with chronic studies including oral toxicity and toxicity following inhalation and insufflation of these compounds. Many methods, such as polarographic studies, fluorometric determinations of uranium, and fluoride analyses, are taken up in detail. Part 4, (Chapters 23-28), Mechanism and Metabolic Studies, takes up bone deposition of uranium and inhibition of carbohydrate metabolism by solutions of hexavalent uranium. The studies include the effect of uranium on excretion of amino acids in urine, treatment of systemic uranium intoxication in rats with British Anti-Lewisite, maximum allowable concentration of insoluble and soluble uranium compounds in air, biological half life of uranium in lung and the lung retention of uranium tetrafluoride. A literature review of the biological effects of uranium on plants and a bibliography of the biological effects of uranium are given. Studies on the inhalation toxicity of boron halides and boron metal were made. In Chapter 29, Dr. Hodge presents a résumé of the work which should be of great value to those who cannot afford the time for a careful reading of the complete work. These volumes should be in every reference library. However, it is felt that this work is beyond the needs of most physicians. M. O.

THE CONCEPTION OF DISEASE. BY WALTHER RIESE, M.D. Pp. 120. New York: Philosophical Library, 1953. Price, $3.75.

FROM this title one might expect most any approach to the various concepts of disease through the centuries. It is difficult to ascertain just what method the author pursues, as he gives no explanation; a short paragraph on the cover flap is the only light shed on the subject. The author's vocabulary, too, is a further handicap. Two illustrations of this are "conception" with its immaculate connotation, and "versions" which suggests operative gynecology. One could hunt longer than the subject warrants to find how this word is used here. No sooner has one found with relief that "concept" is used throughout the Foreword, than the obscurity of style is once more illustrated by the opening sentence: "A concept cannot be made the subject of a tale; it has to be analyzed." In later chapters "conception" again appears through the text.

Chapters on the Stoic concept, the Platonic or cosmological and the anthropologic concept (the Hippocratic with Rousseau's antithesis) permit glimpses of familiar ideas, though almost submerged by obscurities and irrelevancies. One's doubts are strengthened by a brief and questionable presentation of the humoral theory, and of the Hippocratic, which now appears as the historic concept of disease. The Galenic or physiologic concept, we read, "implies a genetic constituent, namely the history of disease." We should make all due allowance for the difficulty of writing in a language with which the author has probably not been long familiar; he was previously affiliated with the Medical Faculties of Frankfurt A/M., and Lyon and with the Sorbonne. Yet even so, the suspicion will not down that the book has been carelessly thrown together, thus exaggerating obscurities of style and thought. In the middle third of the book, brief chapters on the anatomic, physiologic, and etiologic concepts of disease are more intelligible and factual and less

weighed down with side trips into poetry and philosophical observations that to this reviewer at least add nothing and actually detract from the presentation.

This book is appropriately published by the Philosophical Library, as it will undoubtedly mean more and have more appeal to the philosophical than the medical reader.

E. K.

PERSONALITY DEVELOPMENT IN ADOLESCENT GIRLS. BY LAWRENCE K. FRANK, ROSS HARRISON, ELISABETH HELLERSBERG, KAREN MACHOVER AND META STEINER. Pp. 316; 25 ills. New Orleans: Child Development Publication of the Society for Research in Child Development, Inc., 1953. Price, not given.

THIS is a volume showing how much help modern psychological techniques and their intelligent interpretation can be to guide us in our educational planning for mature personality development. The study was undertaken to explore the personality reactions of girls just before, during, and after puberty by their responses to a number of projective techniques. The investigators also worked to show what each test could uniquely contribute. They wished to find out about the inner world of these girls, how they feel and think about themselves and their ways of living, what they fantasy, and what they believe and expect. More specifically, this study was focused upon the psychological maturation of the adolescent girl, her image of the self and of her body, her acceptance or rejection of being female and of the feminine role, her relations with and feelings toward her parents and toward boys, her anxieties and her feelings of guilt, her hopes and fears, and how she is facing the inescapable life tasks of adolescence in our changing culture today. Also, it attempted to discover the personality, character-structures and modes of expression, of repression, and of defense used by these girls.

This they accomplished with four tests, Thematic Apperception Test, Horn-Hellersberg Test, Human Figure Drawings and Rorschach and Graphology. The method of using the tests is described and sample records are given.

The chapter on interpretive summary findings is complete and interesting and we quote the following paragraph from it: "Acceptance of the feminine role is still not yet reached by most of the adolescent girls. Those from the lower social-economic level who have not been traumatized by the home-neighborhood come closest to a mature acceptance of the feminine role. In some, intellectual striving and careering appear to be compensations for frustrated or unacceptable femininity. Wide variations are observable among girls in different schools and colleges, some being already committed to jobs and careers with various versions of being feminine; others are romantic and glamor minded; some are coquettishly affected and inclined to sentimental, romantic definitions of the feminine role."

A valuable part of the volume is a chapter entitled "Suggestions for Schools and Agencies" in which the author says: "As the findings of this study indicate, the adolescent girl finds great difficulty in clarifying what the feminine role means and discovering how to play that role in ways that are congruent to her own individual needs and capacities. No one can teach girls what feminine role they should accept today when there is so much confusion over this; but schools can help girls to discover what different conceptions of the feminine role involve, what are the costs and advantages of being a woman today and following various patterns, including the dual responsibilities of families and outside jobs.

"Observation and actual care of young children in homes and in nursery schools are also desirable since girls coming from small families today often have little or no experience with young children. Moreover, as they participate in nursery schools they often gain many insights into their own personality needs and emotional reactions."

Valuable alike for the psychologist, psychiatrist and educator. Here is a wealth of nontechnical material for the thoughtful socially minded individual.

O. E.

GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY. BY PETER HERBUT, M.D., Jefferson Medical College. Pp. 683; 428 ills. Philadelphia: Lea & Febiger, 1953. Price, $12.50.

THERE are available for most of the special branches of medicine, texts of the pathology of that particular specialty. Until recently there has been but one standard text in the pathology of gynecology and obstetrics. Dr. Herbut has added a second, a text of greater completeness and practicability. He has used the familiar style of treating each anatomic area separately and following the rigid sequence of definition, incidence, cause, gross appearance, microscopic appearance, complications, clinicopathological correlation, diagnosis, treatment and prognosis in its discussion. This method may be criticized for its tendency to become uninteresting and repetitious

but there can be little argument that it makes every subject readily available. Some might question the advisability of a pathologist writing upon the diagnostic and therapeutic aspects of the conditions he discusses.

The chapter on physiology is written by Dr. A. E. Rakoff. It is excellent but in the opinion of this reviewer too brief for the extent of its importance in a discussion of the general subject matter.

The chapter on cytology is also contributed by Dr. Rakoff. It is essentially an evaluation of the method and not a guide for its use and interpretation.

A chapter on the Rh factor and another on the anemias of pregnancy are written by Dr. L. A. Erf. The remainder of the text is a detailed discussion of the common and rare conditions which affect the female genital system. It is essentially a thorough review of what has been written on the subject. The bibliography is imposing and it should stimulate a wide circulation among all those interested in the general or special practice of medicine. E. A.

EMOTIONAL FACTORS IN SKIN DISEASES. By ERIC WITTKOWER, M.D., Assistant Professor of Psychiatry, Allan Memorial Institute of Psychiatry, McGill University; and BRIAN RUSSELL, M.D., Skin Department, The London Hospital. Pp. 214. New York: Paul B. Hoeber, Inc., 1953. Price, $4.00.

A PERSON who has been interested in the field of emotional factors in skin diseases for more than 20 years can not help but admire and welcome Wittkower and Russell's production. Written by a psychiatrist and a dermatologist, we have at last an integrated, comprehensive and reasonably objective discussion of this controversial subject. Furthermore, the statements from the literature are substantiated and refuted by controlled data from the authors' experience.

This book consists of two parts and an index. The first part is an adequate general discussion of the psychosomatic approach to skin diseases, developmental neuroanatomy and physiology of the skin, and investigation and management of patients with skin diseases. The second part discusses skin diseases in which psychosomatic factors are of particular importance, both abnormal skin sensations and abnormal skin manifestations. There are certain omissions in this section. The authors have recognized this but felt that their case material on these disorders was not large enough to draw definite conclusions. The skin and psychoses are also given attention. Authors and subjects covered are well indexed.

Despite any deficiencies that one may find in this work, it is a real contribution to the field and merits serious consideration by all physicians, not only by psychiatrists and dermatologists. H. B.

THE GOLD-HEADED CANE. By WILLIAM MACMICHAEL, M.D. A new edition with a Foreword by JAMES J. WARING, M.D. and a Preface by WILLIAM J. KERR, M.D. Pp. 185; 40 ills. 7th ed. Springfield, Ill.: Charles C Thomas, 1953. Price, $6.50.

THIS latest edition, with text and illustrations taken from Peachey's fifth edition (1923) now appears with new Foreword and Preface, and annotations conveniently distinguished from Peachey's by the use of italics.

Not only is there, fortunately, a continuing demand for this witty, readable and informative bit of medical history literature, but an added item in its favor is to be found in Dr. Kerr's description of a modern Gold-Headed Cane awarded annually to an outstanding physician who addresses the University of California during graduation week on some medical history topic. It has now been given 14 times since 1939. The new cane closely resembles the original in the Royal College of Physicians, though permission to use this original for an exact copy could not be obtained. Its cross handle is hollow and contains an illuminated scroll, with the name of the recipient engraved on the removable threaded endpiece, replacing each year a temporary scroll containing the names of two students who have been honorably mentioned.

The book, therefore, should be of value in stimulating interest in historical and cultural aspects of medicine, especially on the Pacific Coast, where such efforts have already succeeded in bringing "the Art of Medicine more forcibly" before medical men. E. K.

PATHOLOGY OF THE HEART. Edited by S. E. GOULD, M.D., D.Sc., Clinical Professor of Pathology, Wayne University College of Medicine, Detroit. Pp. 1023; 411 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $25.50.

THE editor of this volume, with the aid of 13 outstanding collaborators, has made an excellent contribution to cardiac literature in a day when very rapid advances are occurring

and when a very real need is felt for a compilation of authoritative information in readily available form. The book is designed for both the pathologist and the clinician. In each chapter there is integrated that broad concept of cause, form, and function which modern pathology requires, and which is so much more useful to the clinician. Beginning with a chapter on the history of the pathology of the heart, there follow chapters on the development of the heart, its structure in the adult, the physiology of the heart, congenital malformations, degenerative diseases, vascular lesions, rheumatic disease, non-rheumatic inflammatory diseases, parasitic involvement, injuries by physical violence, neoplasms, clinicopathologic correlations, and methods of gross examination. An excellent bibliography is included with each chapter, the references being arranged for each subject according to the date of publication. This is supplemented by an index of authors at the end of the volume as well as by a complete subject index. The excellent illustrations which are very well reproduced (except for a failure of proper color superimposition on page 106) add much to the value of the volume, and have been responsible, no doubt, for the high price asked for the book. The book is highly recommended to cardiologists, internists, and cardiac surgeons as an excellent supplement to clinical cardiac texts. T. D.

NEW EDITIONS

The Autonomic Nervous System. By Albert Kuntz, Ph.D., M.D., Prof. of Anatomy, St. Louis University School of Medicine. 4th ed. Pp. 605; 94 ills. Philadelphia: Lea & Febiger, 1953. Price, $10.00.

The 4th edition of this work has been extensively revised and brought abreast with current knowledge. While most of the recent material is covered in new references, it is to be regretted that much of the older bibliography has been omitted. Those who use this work have in the past appreciated the extensive bibliography in the 3rd edition, yet over three-fourths of these references have been deleted. The numerous illustrations are better than those of the former edition. D. K.

Diseases of the Liver, Gallbladder and Bile Ducts. By S. S. Lichtman, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College. 3rd. ed. 2 volumes. Pp. 1315; 220 ills., 3 plates in color. Philadelphia: Lea & Febiger, 1953. Price, $22.00.

The recent years have seen rapid advances in our knowledge of liver function and of diseases that involve the liver and bile passages. The profession will, therefore, all the more welcome the new, thoroughly revised third edition of this text. Particularly to be commended are the numerous good illustrations and the handy format in two volumes with a complete index in each. R. K.

Essential Urology. By Fletcher H. Colby, M.D., Associate Professor of Genito-Urinary Surgery, Harvard Medical School, and Chief of the Urological Service. Massachusetts General Hospital. 2nd ed. Pp. 650; 352 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $8.00.

This is the second edition of an excellent text for students and residents in urology. The original material has been amplified to include the more recent contemporary work in this field, particularly with reference to cancer of the prostate, and genito-urinary tuberculosis. K. C.

Rheumatische Erkrankungen. By Prof. Dr. Max Hochrein. 2nd ed. Pp. 416; 121 ills. Stuttgart: Georg Thieme Verlag, 1952. Price, DM 36.

This is the second edition of this German work, written for the practitioner and keeping in mind the practical aspects of the diagnosis and management of the rheumatic diseases. The presentation is sound and adequate. References include a fair number of publications in the non-German literature, although the coverage is by no means complete. There are numerous and good illustrations. R. K.

Your Arthritis. By Alfred E. Phelps, M.D., 2nd ed. Pp. 192; 10 ills. New York: William Morrow & Co., 1953. Price, $3.00.

Dr. Phelps has rewritten and brought up-to-date his excellent manual on arthritis and related diseases. The book is written for the layman and succeeds in its aim to give him the pertinent medical facts which will assist him in the intelligent management of his disease. The quality of the book, however, is such that it may also be read with interest by doctors whose work has not brought them into daily contact with the problem of rheumatism. J. L.

Textbook of Exodontia. By Leo Winter, D.D.S, M.D. Revised by William F. Harrigan, D.D.S., M.D., Prof. of Oral Surgery, New York University, and Leo Winter, Jr., D.D.S., Visiting Oral Surgeon, Bellevue Hospital. 6th ed. Pp. 350; 385 ills., and 1 color plate. St. Louis: C. V. Mosby Co., 1953. Price, $8.00.

This text dealing with tooth extraction and associated problems covers 350 pages and 385

illustrations with one color plate. It is primarily a text for dental students and general dentists.

Chapter I covering examination and diagnosis is of particular interest emphasizing as it does the importance of a correct diagnosis based upon adequate history and a careful examination. The authors lay particular stress on obtaining an adequate history prior to surgery, and point out many pitfalls the exodontist may avoid by obtaining a brief but pertinent history prior to surgery.

The book tends to overly emphasize the value of local anesthesia and has omitted any guide to general anesthesia which is so necessary in the practice of exodontia.

Chapter X is particularly valuable to the general dentist and warns against extraction of a third molar tooth during the acute inflammatory process known as pericoronitis.

Chapter XII dealing with chemotherapy and antibiotics in exodontia practice is well written and a timely explanation of the valuable aid these various agents are to the dentist.

The radiographs and drawings are generally good. The lines of incision in designing flaps could be improved upon.

The book is recommended as a concise reference for those interested in the practice of exodontia. J. C.

NEW BOOKS

Guide for National Studies of Nursing Resources. By MARGARET G. ARNSTEIN, R.N., M.P.H., Chief, Division of Nursing Resources, U. S. Public Health Service. Pp. 36. Geneva: World Health Organization, 1953. Price, $.20.

THE plan outlined in the guide is designed to assist nations in a study of their own nursing services. It is specific enough to be of real value to any committee or group which desires to study the general nursing situation in any area. H. B.

Psychoanalysis and Personality: A dynamic theory of normal personality. By JOSEPH NUTTIN, Professor at Univ.. of Louvain. Pp. 310. New York: Sheed and Ward, 1953. Price, $4.00.

THIS is a book by a man who is a student both of religion and modern dynamic psychology. He discusses Freud, Adler, Alexander and Rogers and attempts eventually a theory of normal personality which integrates both psychology and "higher" aspirations. The author suggests the term *needs* in place of instincts and indicates that man has needs not only at the biochemical level but at the spiritual level as well. "These different forms of need are involved with each other to form complex 'motives' that release and govern human behavior." The author accepts the importance of modern dynamic psychology in man's planning and pleads for psychology and religion to complement each other. O. E.

The Epidemiology of Health. A New York Academy of Medicine Book. Edited by IAGO GALDSTON, M.D. Pp. 197. New York: Health Education Council, 1953. Price, $4.00.

EPIDEMIOLOGY has for a long time carried the connotation of mass disease; although the word itself simply denotes study and knowledge of groups or crowds. This excellent book, by fourteen contributors, clearly presents the natural history of health with practical suggestions on how the objective of health in the mass can effectively be achieved. An epidemiology of health is already pursued in obstetrics, pediatrics, the U. S. Army and, to a lesser extent, in American industry. But it has the promise of extending rapidly into the fields of individual and community health through behavior-centered health education. J. K.

Child Psychology. BY LESTER D. CROW and ALICE CROW. Pp. 267; illustrated. New York: Barnes & Noble, Inc., 1953. Price, $1.50.

THIS volume condenses the essentials of child psychology and represents the summarization of seventeen leading textbooks on the subject. It follows a pattern of progressive psychological growth from infancy through early adolescence. Prepared primarily for the college student, it has a set of true-false questions for each chapter as well as over-all questions which are a help in fixing in mind what has been learned.

A great deal of valuable material is presented in a condensed form. It lacks a psychoanalytical orientation which will represent a definite deficiency for many readers. O. E.

Transactions of the American College of Cardiology, Volume 2. Edited by BRUNO KISCH, M.D. Pp. 252; 43 ills. New York: American College of Cardiology, 1953. Price, $5.00.

THIS publication is a record of the papers presented at the American College of Cardiology at two meetings during 1952. The theme of the meeting in June is the treatment of the cardiac and that of the meeting in Novemberr is the methods of graphic registration of cardiac events.

The majority of authors have submitted a written report of their presentations. The topics are concerned with problems of current interest. Many of the viewpoints expressed are controversial and challenging. J. Z.

Bioassay of Anterior Pituitary and Adrenocortical Hormones. Volume 5. Edited by G. E. W. WOLSTENHOLME, General Editor for the Ciba Foundation. Pp. 228; 53 ills. Boston: Little, Brown & Co., 1953. Price, $6.00.

AN eminent group of investigators have collaborated to produce an extremely valuable contribution to the field of investigative endocrinology. The latest methods of assaying anterior pituitary and adrenocortical hormones are described. This volume will be of interest primarily to laboratory workers and research clinicians. W. P.